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THEORY OF GASTRIC FUNCTION

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On the basis of some assumptions concerning gastric emptying a theory of gastric function is developed which explains the known facts —chiefly the emptying of liquids according to an exponential law. On the basis of this theory an equation is derived which relates the rate of secretion to the quantity of liquid retained in the stomach after a certain time. A study is made of the general characteristics of this equation. Some assumptions concerning different formulae describing the rate of secretion are found useful in experimental investigations, particularly in Hollander's dilution indicator method.

One of the authors (Salamanca, 1943) has developed a method which allows us to determine the amounts of tea and gastric juice retained at any time after the ingestion of a quantity of tea. The continued use of this procedure over a period of many years has resulted in a great number of observations which require a theory of the gastric function for their correct interpretation. Such a theory is developed in the present paper.

Schematically the function of the stomach consists in merely receiving a certain alimental volume (in exploratory tests, 250 cc. of tea) and in emptying it slowly, mixed with a gastric secretion, which contains hydrochloric acid, chlorides and ferments as essential elements. In practice, in order to characterize the composition of gastric juice, it is sufficient to determine the concentration of hydrochloric acid and of total chlorine; the determination of the ferments in the contents is not usually made in the clinic.

We denote the volume of tea retained by the stomach by a function of time, $R(t)$, the quantity of gastric juice secreted between the time of ingestion and time t by $f_1(t)$ and the juice retained by the stomach in time t by $f_2(t)$.

We will first study gastric emptying, which is the result of stomach motility, and afterward the secreting function, distinguishing between total secretion and secretion of the specific elements, hydrochloric acid and total chlorine.

I. *Theory of Gastric Emptying.*

The two initial hypotheses of our theory are the following:

a) The pylorus receives a stimulus every u seconds to which it is able to respond in two ways—opening or not opening. The first response has a probability p and the second the probability q, $(p + q = 1)$.

b) Each time the pylorus opens, the stomach empties a constant fraction c of its contents.

With these two hypotheses we are able to characterize the function $R(t)$. Let us suppose that 250 cc. of tea have been taken in. After the first opening of the pylorus, there will remain in the stomach

$$250 - 250\,c = 250\,(1 - c) \text{ cm}^3 \text{ of tea}.$$

After the second opening there will remain

$$250\,(1 - c) - 250\,(1 - c)\,c = 250\,(1 - c)^2,$$

and so on. After the nth pyloric opening there will be left in the stomach a quantity of tea

$$R(t) = 250\,(1 - c)^n. \tag{1}$$

When n becomes sufficiently large with respect to c, (1) will be approximately equal to

$$R(t) = 250\,e^{-cn}, \tag{2}$$

and as n is proportional to t we may finally write

$$R(t) = 250\,e^{-kt}. \tag{3}$$

Thus $R(t)$ is a decaying exponential function of time. This has been confirmed by experiment in extractions made within 30, 60, 90, 120, 150 and 180 minutes after the intake of a test meal (Salamanca, Garcia Morato and Delgado, 1945). The value of the constant k is 0.0284 for a normal adult and 0.0213 for a normal child (Salamanca and Tamarit, 1948a).

Hypothesis a) has also been verified by experiment. The pyloric opening was observed radiologically (Tamarit and Truchuelo, 1948). Using a reasoning similar to the one used by E. Marsden and T. Barrat (1911) in the study of the emission of corpuscles by radioactive atoms, it is possible to calculate the probability that the interval between two consecutive pyloric openings will be greater than a given interval τ. Actually the pylorus will receive during this time a number of stimuli equal to $\varepsilon(\tau)$ and the probability sought is approximately

$$P = e^{-p\varepsilon(\tau)},$$

where p, it will be recalled, is the probability that the pylorus opens upon receiving a stimulus.

In the paper of J. T. Tamarit and J. Truchuelo (1948) an interesting fact was encountered, namely, the existence of a refractory time (ρ) in pyloric functioning. Thus after each pyloric opening there is a time of ρ seconds during which no stimulus reaching the pylorus can be effective. Taking the existence of this refractory phase into account, the number of stimuli reaching the pylorus during time τ will be

$$\varepsilon = (\tau - \rho)/u,$$

and the probability sought is

$$P_\varepsilon = e^{-p(\tau-\rho)/u}.$$

The theoretically calculated probability agrees satisfactorily with the values actually found. In the above observations it was found that for the normal stomach the following values hold

$$p/u = 5.91 \times 10^{-2}\ \text{sec}^{-1}; \qquad \rho = 5.14\ \text{sec}.$$

The average number of pyloric openings (n) occurring in time t is

$$n = \frac{t}{u/p - \rho} = t/22.06.$$

Thus if the tea meal is tested in different persons and the extraction of the gastric contents is done at the same interval of time after ingestion, the quantities of tea retained will depend chiefly on the number of times the pylorus has opened. The quantity of the tea retained must therefore be related to the distribution of frequencies of the number of favorable cases of a phenomenon (pyloric opening) having a small probability (p), i.e. according to Bortkiewicz-Poisson's law. This has been confirmed by J. T. Tamarit (1947) through the results of investigations carried out on adults and children.

As to the value c, which might be called "emptying gastric power," there is to date no definite method for determining it. Assuming the rate of pyloric opening to be the same for tea as for barium substance used for roentgenologic observation, the value of c might be calculated indirectly. One thus obtains the value $c = 0.0104$, that is, the stomach empties 1.04 per cent of its contents upon each caloric opening. Further investigations have been undertaken.

II. *Theory of Gastric Secretion.*

The first problem is to find the relation between quantities secreted and quantities retained by the stomach.

We assume that gastric emptying is performed according to equation (3). Differentiating equation (3) we have

$$\frac{dR(t)}{dt} = -k \cdot 250\, e^{-kt} = -k \cdot R(t).$$

Now we shall consider the volume of secreted liquid.

III. *Secretion of Gastric Juice.*

According to our notation the quantity of gastric juice retained in the stomach during the time t is $f_2(t)$. In an infinitesimal interval of time, dt, the variation in the amount of gastric juice retained, which is $f_2'(t)\,dt$, will be equal to the volume secreted in this interval $[f_1'(t)\,dt]$ less the quantity of juice that has been emptied $[k \cdot f_2(t) \cdot dt]$. We may thus postulate the following differential equation:

$$f_2'(t) = f_1'(t) - kf_2(t). \tag{4}$$

This gives

$$f_2(t) = e^{-kt}\left[\int e^{kt} f_1'(t)\,dt + C\right], \tag{5}$$

where C is a constant of integration. Imposing initial conditions so that $f_2(t) = J_0$ for $t = 0$ (J_0 = gastric juice contained in the fasting stomach), we have

$$f_2(t) = e^{-kt}\left[\int_0^t e^{kt} f_1'(t)\,dt + J_0\right]. \tag{6}$$

The solution of the integral of (6) depends on the form of the function $f_1(t)$.

In the simplest case $f_1'(t)$ = constant = v_0, and equation (6) takes the form of

$$f_2(t) = v_0(1 - e^{-kt})/k + J_0\, e^{-kt}. \tag{7}$$

In this case the quantity of juice retained in the stomach will increase with time approaching a limit,

$$\lim_{t=\infty} f_2(t) = v_0/k. \tag{8}$$

Thus if the stomach secretes at a constant rate, an equilibrium condition will be reached with the quantity of retained juice equal to v_0/k. At this time the secretion rate and the emptying rate are equal.

This is what occurs in the resting stomach during fasting. According to K. Faber (1935), one can extract from a normal person a quantity of juice of approximately 20 to 50 cc., which corresponds to a resting secretion rate of .57 to 1.42 cc. per min. respectively. We have calculated an average value of 1.07 cm^3/min. for adults and 0.21 cm^3/min. for children (Salamanca and Tamarit, 1948b).

If the condition of gastric rest is altered by a stimulus (tea or test meal, histamine, insulin, etc.), we have a different situation. However, even under such circumstances one may proceed within short intervals of time as if the rate of secretion were constant, as some authors have done (Hollander and Penner, 1940; Schoen and Knoefeld, 1947; Schoen and Griswold, 1947). Their results ought to be considered only as first approximations, especially because they make the additional hypothesis that the rate of emptying is also constant during the period of observation. With our theory one obtains a better approximation to reality.

Before making any complementary hypothesis on the form of the function $f_1'(t)$ in the active stomach, it is most convenient to study the conditions of maximum and minimum of the function $f_2(t)$. Differentiating equation (6) we have:

$$f_2'(t) = -kf_2(t) + f_1'(t); \tag{9}$$

$$f_2''(t) = -kf_2'(t) + f_1''(t) = k^2 f_2(t) - kf_1'(t) + f_1''(t). \tag{10}$$

In order that $f_2(t)$ has a maximum, we must have

$$f_1'(t) = kf_2(t)$$

and also

$$f_2''(t) = f_1''(t) < 0.$$

Similarly for the amount of juice retained to be a minimum, we must have $f_1'(t) = kf_2(t)$; $f_2''(t) = f_1''(t) > 0$.

Experimentally it is not possible to make direct determinations of $f_1'(t)$ and we only have a direct knowledge of $f_2(t)$; thus the experimental observations are useful to deduce consequences about $f_1'(t)$ from the known values of $f_2(t)$. This function has been studied experimentally by F. Enriquez de Salamanca and J. Picazo (1943) in adults and by F. Enriquez de Salamanca, V. Garcia Morato and C. Perez Delgado (1945) in children. From these observations one deduces that the function $f_2(t)$ at first increases, attains its maximum within 60 minutes, then decreases to attain a minimum within about

120 minutes, and afterward it increases again. No observations have been made in times greater than 150 min., but it is plausible to suppose that the function will have another maximum and afterward will diminish asymptotically to again attain its resting value. In children the function $f_2(t)$ behaves similarly with the difference that the minimum is attained within 150 min. The maximum value of the juice retained in adults is about 168.33 and in children 28.57 cc.

According to the above conditions, necessary for the existence of turning points of the function $f_2(t)$, we have that within 60 min. the rate of secretion has to be 4.78 cc. per min. ($= 0.0284 \times 168.23$) and in decreasing phase. Since the resting rate is 1.07 cc. per min. it must, of course, have passed through a maximum before the 60 min. Within 120 min. in adults the secretion rate must be 2.54 cc. per min. ($= 0.0284 \times 89$) and in increasing phase; thus it must have passed through a relative minimum. After the 120 min. the secretion rate will continue increasing, it will pass through another maximum and then it will diminish tending asymptotically toward the value at rest. Similar deductions can be made referring to children.

In short, the conditions imposed by observations on the function $f_1'(t)$ during the digestive process are:

1. The function $f_1'(t)$ tends to approach the value of the secretion rate at rest,

$$\operatorname*{Lim}_{t=\infty} f_1'(t) = v_0.$$

2. The function $f_1'(t)$ must be such that it makes $f_2(t)$ twice maximum once within 60 min. and the second time within 150 min. more or less. It must also have the property to make $f_2(t)$ minimum at about 120 min.

3. The function $f_1'(t)$ must have a maximum (absolute or relative) between 0 and 60 min., a relative minimum between 60 and 120 min. and a relative maximum at about 150 min.

We believed this digression necessary first as an orientation for the empiric investigator (physiologist, experimental pathologist) and secondly as a point of departure for new researches that might be undertaken to resolve important questions of the gastric physiology.

In the following some interesting hypotheses are considered in relation to the imposed conditions.

First Hypothesis. Let us suppose that

$$f_1'(t) = v_0 + v_1 e^{-k_2 t} \tag{11}$$

and, in the most common case, let us suppose that k_2 be distinct from the constant of emptying, which we will designate by k_1. The gastric response consists actually in these cases of a sudden increase followed by a slow decrease, and discounting the first short phase, the rest may be represented by an exponential function of the type (11). A similar thing is done by N. Rashevsky (1938) studying the delayed reflex.

It can easily be seen that this hypothesis satisfies condition 1.

Substituting (11) into (6) we have

$$f_2(t) = v_0/k_1 + v_1(e^{-k_2 t} - e^{-k_1 t})/(k_1 - k_2), \tag{12}$$

and its derivative is

$$f_2'(t) = v_1(k_1 e^{-k_1 t} - k_2 e^{-k_2 t})/(k_1 - k_2), \tag{13}$$

which vanishes for the following value of the time

$$\theta = \frac{\log k_1 - \log k_2}{(k_1 - k_2)}. \tag{14}$$

Since $f_1''(t) < 0$, in that moment there is a maximum for $f_2(t)$ and thus condition 2 is partly satisfied. In order that the maximum coincides with 60 min, we must have, taking into account the value of k_1 in normal adults, $k_2 = 0.0083$.

With this first hypothesis the moment of the maximum of $f_2(t)$ does not depend upon v_1, but on the constants k_1 and k_2 according to formula (14). The time θ is equal to 60 min. when $k_2 = 0.0083$; it decreases with increasing k_2 and has a minimum when $k_2 = k_1$, then it increases again.

Substituting (14) into (12) we find that in the maximum the quantity of gastric juice retained will be

$$f_2(\theta) = v_0/k_1 + (v_1 e^{-k_1 t})/k_2, \tag{15}$$

a value that depends directly on v_1. In order that in a normal adult the maximum of juice be 170 cc. of gastric juice retained within 60 min. it is necessary that v_1 be equal to 6 cm^3/sec. This would be the initial secretion rate according to (11) and its highest value in the course of the digestive process.

The case in which k_1 and k_2 are equal deserves special consideration. It is easy to see that

$$f_2(t) = v_0(1 + e^{-kt})/k + v_1 t e^{-kt}, \tag{16}$$

and the maximum of $f_2(t)$ is now attained in the time

$$\theta = 1/k.$$

This value θ is also obtained putting $k_2 = k_1$ into formula (14) and applying l'Hopital's rule. In this case the maximum would be attained, taking the normal value of k_1 into account, within 35.21 min. in the normal adult and within 46.95 in the child.

This hypothesis does not satisfy all of the above conditions; it fails because it does not make $f_2(t)$ minimum within 120 min. nor is there a maximum after 150 min.

Second Hypothesis. Let us suppose that

$$f_1'(t) = v_0 + \frac{F_1}{\sqrt{2\pi}} e^{-\frac{(t-t_1)^2}{2\sigma_1^2}} + \frac{F_2}{\sqrt{2\pi}} e^{-\frac{(t-t_2)^2}{2\sigma_2^2}}. \qquad (17)$$

According to this hypothesis, the secretion rate is represented by two waves superposed upon the resting secretion rate, each of which is a normal Gauss curve. This hypothesis is plausible on the following grounds. The secretion of gastric juice is the result of the activity of several glandular units. It may be supposed that they do not all function simultaneously, but that the number acting in any interval of time is expressed by the normal probability function, and the quantity of juice secreted is proportional to the number of units acting. The factors F_1 and F_2 in this hypothesis are related to the total number of secretory units present in the stomach and to the secretion rate of each isolated secretory unit.

In our analysis we assume for simplicity that $\sigma_1 = \sigma_2$. In what follows we show that the conditions imposed upon the function $f_1'(t)$ are satisfied with this hypothesis and the facts established by the empiric observation are accounted for.

Putting (17) into (6) we have

$$f_2(t) = v_0/k + \frac{F_1 \sigma e^{\beta_1} e^{-kt}}{\sqrt{2\pi}} \int_{z_0}^{z} e^{-z^2/2}\, dz + \frac{F_2 \sigma e^{\beta_2} e^{-kt}}{\sqrt{2\pi}} \int_{z_0'}^{z} e^{-z^2/2}\, dz, \qquad (18)$$

where

$$\begin{aligned} z &= (t-\alpha_1)/\sigma; \quad \alpha_1 = t_1 + k\sigma^2; \quad \beta_1 = k(t_1+\alpha_1)/2; \\ z' &= (t-\alpha_2)/\sigma; \quad \alpha_2 = t_2 + k\sigma^2; \quad \beta_2 = k(t_2+\alpha_2)/2. \end{aligned} \qquad (19)$$

It is easy to see in (18) that if t increases indefinitely the last terms of the sum tend to vanish, so that for $t = \infty$, $f_2(t) = v_0/k$, i.e., condition 1 is fulfilled.

As to condition 2 it is always satisfied when t_1 and t_2 are sufficiently separated so that in the first moments the secretion rate is only expressed by the first two terms of (17) and afterward by the

first and third. Referring thus to the beginning of the digestive process we have

$$f_2(t) = v_0/k + F_1\,\sigma\,e^{\beta_1}\,e^{-kt}\left[\frac{1}{\sqrt{2\pi}}\int_{-\infty}^{z} e^{-z^2/2}\,dz - \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{z_0} e^{-z^2/2}\,dz\right], \quad (20)$$

where we may neglect the second integral as z_0 is always greater than 2. Moreover if we replace the first integral by the tangent at its inflection point we have

$$f_2(t) = v_0/k + F_1\,e^{-kt}\,e^{\beta_1}\,[0.3989\,(t-\alpha_1) + 0.5\,\sigma]. \quad (21)$$

Making the derivative of $f_2(t)$ equal to 0 we find that this function attains its maximum in the moment

$$\theta = 1/k + \alpha_1 - 1.253\,\sigma \quad (22)$$

if the maximum coincides with 60 min. Then we have

$$k\,\sigma^2 - 1.253\,\sigma + t_1 + 1/k - 60 = 0\,. \quad (23)$$

This equation gives us the relation that ought to exist between the values t_1 and σ. For each value of t_1 two values of σ are solutions of (23). In order that the values of σ be real it is necessary that

$$4.3782 - 4\,kt_1 \geq 0\,,$$

i.e., that t_1 be less than or equal to 38.62 min. We shall only consider the case in which $t_1 = 38.62$ which gives one value for σ. In that case we find $\sigma = 22$ min. Substituting these values into (19) we have

$$\alpha_1 = 52.45; \qquad \beta_1 = 1.293\,.$$

Replacing the two known values in (18), putting $t = 60$, at which time $f_2(t)$ has its maximum, ignoring the second integral, and calculating the first between $z_0 = -2.38$ and $z = 0.32$ by means of A. L. Bowley's tables (1920) we obtain

$$170 = 37.7 + 9.35\,F_1; \qquad F_1 = 14.1\,.$$

We also may calculate F_1 if we substitute the known values in (17) bearing in mind that $f_1'(60) = 4.83$.

$$4.83 = 1.07 + 0.2492\,F_1; \qquad F_1 = 15.1\,.$$

The difference between the values of F_1 is due to our approximation. We shall take for the value of F_1 the average of the two results $= 14.6$.

To continue our analysis in the vicinity of 120 min. we may develop $f_2(t)$ in Taylor's series, bearing in mind that within 120 min. the function $f_2(t)$ has a relative minimum (= 89 cc.) and thus, as shown before, $f_2'(120) = 0$ and $f_2''(120) = f_1''(120)$. Including in the development only the terms of the second degree, we have

$$f_2(t) = f_2(120) + f_1''(120) \cdot (t - 120)^2/2 , \tag{24}$$

i.e., in the vicinity of 120 min. the function $f_2(t)$ may be represented by a parabola. Keeping in mind that within 60 min. the value of $f_2(t)$ is 170 cc. we are able to calculate

$$f_1''(120) = 0.045 . \tag{25}$$

Putting (24) into (6), introducing a slight change and differentiating the two members, we find a fairly exact expression of $f_1'(t)$, valid in the vicinity of 120 min.

$$\begin{aligned} &e^{kt}[f_2(120) + f_1''(120) \cdot (t - 120)^2/2] = \int_0^t e^{kt} f_1'(t)\, dt + J_0 ; \\ &ke^{kt}[f_2(120) + f_1''(120) \cdot (t - 120)^2/2] \\ &+ e^{kt} f_1''(120) \cdot (t - 120) = e^{kt} f_1'(t) ; \\ &f_1'(t) = kf_2(120) + f_1''(120) \cdot (t - 120) \\ &+ kf_1''(120) \cdot (t - 120)^2/2 . \end{aligned} \tag{26}$$

This expression of $f_1'(t)$ tells us that the secretion has a minimum in the time

$$\tau = 120 - 1/k = 84.79 .$$

The value of t_2 may be calculated in the following way: We know that $f_1''(t)$ at 120 min. has a value of about 0.045, calculated in (25); the secretion rate in that time is 2.54 and the secretion rate, due to the first wave calculated by Charlier's tables is 0.02. Thus the secretion rate due to the second wave is 1.45 cc. (1.07 + 0.02 + 1.45 = 2.54). If we differentiate (17) and denote the exponentials by V_1 and V_2 respectively, we have

$$f_1''(t) = -(t - t_1) \cdot V_1/\sigma^2 - (t - t_2) \cdot V_2/\sigma^2 . \tag{27}$$

Substituting the known values when $t = 120$ we have: $0.045 = -1.627/484 - 1.54(120 - t_2)/484$, which gives $t_2 = 135$. Therefore in order that V_2 be equal to 145 within 120 min. it is necessary that $F_2 = 4.58$. Thus the function (17) is completely characterized.

After 120 min. in the first integral of (18) z is greater than 3 and we have

$$f_2(t) = v_0/k + F_1\, e^{\beta_1}\, e^{-kt}\, \sigma + F_2\, e^{\beta_2}\, e^{-kt}[0.3989\,(t-\alpha_2) + 0.5\,\sigma]\,, \tag{28}$$

which is a good approximation for times greater than 120 min. It is easy to see now that after 120 min. the function $f_2(t)$ will pass through a second maximum in the time

$$\theta = \alpha_2 + 1/k - 1.253\,\sigma - \frac{F_1\,\sigma\, e^{\beta_1}}{0.3989\, F_2\, e^{\beta_2}} \tag{29}$$

which, when the known values are substituted, gives 145 min.

The value attained by $f_2(t)$ in this second maximum may be calculated by substituting the value of (29) in (28)

$$f_2(\theta) = v_0/k + 0.3989\, F_2\, e^{\beta_2}\, e^{-k\theta}/k\,. \tag{30}$$

Putting the known values of the constants into this equation, we find that the quantity of juice retained in the stomach at this second maximum must be approximately equal to 97 cc.

This completes the analysis of our second hypothesis. It explains the known facts and fulfills the conditions imposed on the function $f_1'(t)$. There remains the verification of the relation between t_1 and σ, expressed by (23).

Third Hypothesis. In this hypothesis we unite the two former ones, i.e., we suppose that

$$f_1(t) = v_0 + v_1\, e^{-k_2 t} + (F_1/\sqrt{2\pi})\, e^{-\frac{(t-t_1)^2}{2\sigma^2}} + (F_2/\sqrt{2\pi})\, e^{-\frac{(t-t_2)^2}{2\sigma^2}}\,. \tag{31}$$

In this hypothesis the gastric juice secreted during the digestive process is the result of the mixture of four different secretions: (a) resting secretion (v_0); (b) secretory fraction of exponential type; (c) two secretions superposed on the two former ones in the form of two Gauss' curves.

Putting (31) into (6) we have

$$f_2(t) = v_0/k_1 + v_1(e^{-k_2 t} - e^{-k_1 t})/(k_1 - k_2) + \frac{F_1\,\sigma\, e^{\beta_1}\, e^{-k_1 t}}{\sqrt{2\pi}} \int_{z_0}^{z} e^{-z^2/2}\, dz + \frac{F_2\,\sigma\, e^{\beta_2}\, e^{-k_1 t}}{\sqrt{2\pi}} \int_{z_0'}^{z'} e^{-z^2/2}\, dz\,, \tag{32}$$

with the same substitutions as in (19). Referring to the beginning

of the digestive process we may neglect the second integral and simplify the first, as in the former hypothesis. Thus we have

$$f_2(t) = v_0/k_1 + v_1(e^{-k_2 t} - e^{-k_1 t})/(k_1 - k_2) + F_1 e^{-k_1 t} e^{\beta_1}[0.3989(t - \alpha_1) + 0.5\sigma] . \tag{33}$$

Putting its derivatives equal to zero gives

$$f_2'(t) = v_1(k_1 e^{-k_1 t} - k_2 e^{-k_2 t})/(k_1 - k_2) + 0.3989 F_1 e^{-k_1 t} e^{\beta_1} - k_1 F_1 e^{\beta_1} e^{-k_1 t}[0.3989(t - \alpha_1) + 0.5\sigma] = 0 . \tag{34}$$

Dividing both members by e^{-kt} and taking only the first two terms of the following development

$$e^{(k_1 - k_2)t} = 1 + (k_1 - k_2)t \cdots , \tag{35}$$

we get

$$v_1 - v_1 k_2 t - 0.3989 F_1 k_1 e^{\beta_1}(t - \alpha_1 + 1.253\sigma - 1/k_1) = 0 . \tag{36}$$

This relation is verified only in the moment of the maximum, i.e., when $t = 60$. The quantity $\alpha_1 - 1.253\sigma + 1/k$ corresponds to the time in which the maximum of $f_2(t)$ is attained in the former hypothesis. We shall denote it by T and denote the factor $0.3989 F_1 k_1 e^{\beta_1}$ by h . We finally obtain

$$v_1 = h(60 - T)/(1 - 60 k_2) . \tag{37}$$

From this equality one may deduce a consequence for k_2 . If $v_1 > 0$, and if $T < 60$, we must have $k_2 < 0.0117$; if $T > 60$, then $k_2 > 0.0117$.

As in the case of the former hypothesis, we now have the following equation to study the relations between t_1 and σ

$$k_1 \sigma^2 - 1.253\sigma + 1/k_1 + t_1 - T = 0 . \tag{38}$$

The condition for the vanishing of the discriminant is

$$T - t_1 = 21.5 \tag{39}$$

in which case $\sigma = 22$. The value of t_1 remains undetermined. Since in practice one admits the normal curve to have the characteristic of comprising nearly the totality of the observations between -2σ and $+2\sigma$, we assume, in order to take the earlier activity of the glands during the digestive process into account, that $t_1 = 2\sigma$. Any other hypothesis may be made a priori giving rise to new orientations for empiric investigations that may justify with a greater exactitude the relation between t_1 and σ .

Thus we have obtained the following values:

$$t_1 = 44; \qquad T = 65; \qquad \alpha_1 = 57.75; \qquad \beta_1 = 1.445 .$$

To calculate an approximate value of k_2 we shall use the same device as in the former hypothesis. We shall now replace the function $f_2(t)$ by a parabola,

$$f_2(t) = f_2(60) + f_1''(60) \cdot (t-60)^2/2 . \tag{40}$$

Remembering that for $t = 0$, $f_2(t) = 37.7$ cc., we may calculate the value $f_1''(60) = -0.0735$.

Putting (40) into (6) and proceeding as before we find

$$\begin{aligned} f_1'(t) &= k_1 f_2(60) + f_1''(60) \\ &\cdot (t-60) + k_1 f_1''(60) \cdot (t-60)^2/2 , \end{aligned} \tag{41}$$

which shows that the function $f_1'(t)$ passes through a single maximum point at the time $\tau = 60 - 1/k_1 = 24.79$.

That is to say, the function $f_1'(t)$ has a maximum at about 25 min., therefore $f_1''(t)$ must vanish at this moment. Thus differentiating (31), ignoring the last term of the sum, and setting the derivative equal to 0, we get

$$f_1''(\tau) = k_2 v_1 e^{-k_2\tau} - \frac{\tau - t_1}{\sigma^2} \frac{F_1}{\sqrt{2\pi}} e^{-\frac{(\tau-t_1)^2}{2\sigma^2}} = 0. \tag{42}$$

Substituting the known values and replacing v_1 by its value given in (37) we have

$$0.0108 F_1 = 0.3989 F_1 e^{\beta_1} k_1 \cdot 5 k_2 e^{-25k_2}/(60 k_2 - 1), \tag{43}$$

and substituting approximately

$$e^{-25k_2} = 1 - 25 k_2 \cdots ,$$

we finally obtain

$$3.8 k_2^2 + 0.4968 k_2 - 0.0108 = 0 , \tag{44}$$

which gives $k_2 = 0.019$. The other root of k_2 of the equation (44) is negative and must be discarded, since otherwise we would have a secretion which would increase indefinitely in the course of the digestive process.

Substituting the value of k_2 in (37) we have

$$v_1 = 1.082 F_1 ,$$

and putting the same value into (42) results in

$$v_1 = 0.915\, F_1 .$$

We obtain two slightly different coefficients because of the approximate character of some of the substitutions used, but the difference is so small that the reasoning followed is quite justified. We may take the average value, which is approximately unity, i.e.,

$$v_1 = F_1 .$$

The values of v_1 and F_1 can now easily be calculated since they have to be such as to give $f_2(t)$ a value equal to 170 cc. within 60 min. and $f_1(t)$ a value of 4.83 cc./min. in the same time. Substituting the known values in (31) and (32) we have

$$3.76 = 0.6313\, F_1 , \text{ from which } F_1 = v_1 = 5.91 ;$$
$$132.30 = 23.511\, F_1 , \text{ from which } F_1 = v_1 = 5.63 .$$

Taking the average value, we have $F_1 = v_1 = 5.77$.

Now we can calculate each of the values of the fraction of secretion at 120 min. and we find that the value due to the second wave is 0.87 cc./min. By the same process as in the former hypothesis we now calculate t_2 which turns out to be equal to 152 min. The quantity $F_2 = 6.23$, slightly greater than F_1 , but is approximately of the same order.

Herewith we complete the analysis of our third hypothesis, which also explains the known facts of the gastric physiology and which fulfills the conditions imposed on function $f_1(t)$. The analysis of hydrochloric acid and chlorides will be made in a later paper.

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MATHEMATICAL BIOLOGY OF SOCIAL BEHAVIOR: III

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A society composed of individuals each of whom can perform one of two mutually exclusive activities R_1 and R_2 is considered. The tendency toward the performance of those activities is measured by the intensities ε_1 and ε_2 of excitation of two corresponding neural centers, which cross-inhibit each other. It follows from the theory developed by H. D. Landahl that an individual with $\varepsilon_1 - \varepsilon_2 = 0$, that is one who has no preference for either one of the two activities, will on the average perform R_1 and R_2 with equal probability. As $\varepsilon_1 - \varepsilon_2$ increases, the probability P_1 of R_1 increases, tending to 1. As $\varepsilon_2 - \varepsilon_1$ increases, the probability P_2 of R_2 increases, tending to 1. We have $P_1 + P_2 = 1$.

The effect of imitation is now studied. The total number of individuals in the society which exhibits an activity R_1 at a given time is considered as constituting a stimulus which increases ε_1. Similarly, the total number of individuals which exhibits activity R_2 at a given time constitutes a stimulus which increases ε_2. Using the standard equations of the mathematical biophysics of the central nervous system, equations are established which govern the behavior of such a society and the following conclusions are reached.

If the quantity $\varepsilon_1 - \varepsilon_2$ is distributed in the society in such a way that the distribution function is symmetric with respect to $\varepsilon_1 - \varepsilon_2 = 0$, then on the average one-half of the population exhibits R_1, the other half R_2. This social configuration may, however, be unstable. The slightest accidental excess of individuals exhibiting, for example, R_1, may bring it into a stable configuration, in which most individuals exhibit R_1, and only a smaller fraction exhibit R_2. A slight initial deviation in favor of R_2 brings it into a stable configuration, in which most individuals exhibit R_2. Thus in this case there may be two stable configurations. If the population is in one of those stable configurations, and the distribution function of $\varepsilon_1 - \varepsilon_2$ is made asymmetric, favoring the other activity, the population will pass into a stable configuration, in which that other activity is predominant, if the asymmetry of the distribution exceeds a threshold value.

By making some drastic simplifications the equations derived here may be reduced to a form which was *postulated* by the author previously in his mathematical theory of human relations.

Consider a population of N_0 individuals. Let each of them have a tendency to perform two mutually exclusive reactions R_1 and R_2.

These tendencies are measured by the corresponding excitations ε_1 and ε_2 which lead to R_1 and R_2, and which also cross-inhibit each other, as in the neural circuits introduced originally by H. D. Landahl (1938) and used in our preceding paper (Rashevsky, 1949). Whether the reaction R_1 or R_2 is made is determined by the quantity $\varepsilon_1 - \varepsilon_2$ (Landahl, 1938; Rashevsky, 1948b). Therefore we shall consider this quantity $\phi = \varepsilon_1 - \varepsilon_2$. An individual with $\phi = 0$ has an equal tendency to R_1 and R_2, and the probability of either one of them is $\frac{1}{2}$. For $\phi > 0$, the individual has a preference to R_1. The probability P_2 of R_2 tends to zero as ϕ tends to $+\infty$. For $\phi < 0$ the preference is in favor of R_2, and the probability P_2 tends to 1 as ϕ tends to $-\infty$. Let the number of individuals whose ϕ lies between ϕ and $\phi + d\phi$ be given by $N(\phi)\,d\phi$. We have

$$\int_{-\infty}^{+\infty} N(\phi)\,d\phi = N_0. \tag{1}$$

If we consider a sufficiently large number of individuals all with the same ϕ, then at any time a fraction $P_1(\phi)$ of them will perform reaction R_1, and a fraction $P_2(\phi) = 1 - P_1(\phi)$ will perform reaction R_2. Hence, denoting by $x(\phi)\,d\phi$ the number of individuals with a ϕ in the interval between ϕ and $\phi + d\phi$, and performing reaction R_1, we have

$$x(\phi) = P_1(\phi)N(\phi). \tag{2}$$

If $y(\phi)\,d\phi$ denotes the number of individuals in the interval ϕ, $\phi + d\phi$ which performs reaction R_2, we have

$$y(\phi) = P_2(\phi)N(\phi). \tag{3}$$

Now we shall consider the effect of imitation of behavior. When an individual imitates others, this may be interpreted in the following way:

Each other individual performing R_1 acts on the given individual as a stimulus which adds to the excitation ε_1. Each other individual who performs reaction R_2 acts on the given individual as a stimulus which adds to ε_2. The additional amounts ε_1' and ε_2' vary according to the usual differential equation (Rashevsky, 1948b)

$$\frac{d\varepsilon}{dt} = AE - a\varepsilon. \tag{4}$$

We shall consider here the simple case in which the constants A and a are the same for all individuals, regardless of their ϕ. The more general case leads to great mathematical difficulties.

Denoting by X the total number of individuals who perform R_1, and by Y the total number who perform R_2, we have

$$\frac{d\varepsilon_1'}{dt} = AX - a\varepsilon_1' ; \tag{5}$$

$$\frac{d\varepsilon_2'}{dt} = AY - a\varepsilon_2' . \tag{6}$$

Putting

$$\varepsilon_1' - \varepsilon_2' = \psi , \tag{7}$$

we have

$$\frac{d\psi}{dt} = A(X - Y) - a\psi . \tag{8}$$

If the distribution function $N(\phi)$ is symmetric with respect to $\phi = 0$, then, in the absence of external influences, $X = Y$, or $X - Y = 0$. Half of the individuals will perform R_1, the other half R_2. Therefore, according to equation (8), ψ will remain zero.

However let an accidental fluctuation result in a slight excess of X. Then ψ will begin to grow. The quantity which now determines whether R_1 or R_2 occurs is no longer ϕ, but $\phi + \psi$. As $\phi + \psi$ increases, the probability P_1 for each individual to perform R_1 increases. Therefore X increases while Y decreases, so that $X - Y$ increases. Similar considerations hold for an accidental excess of Y. Thus the configuration $X = Y$ for a symmetric $N(\phi)$ may in general be unstable.

To investigate whether a stable configuration exists and to determine it, we must make specific assumptions about $N(\phi)$ and the functions $P_1(\phi)$ and $P_2(\phi)$.

The natural thing to do is to assume $N(\phi)$ to be a normal distribution. This, however, prevents the evaluation of various integrals in finite form. Therefore we shall follow H. D. Landahl (1937) and put

$$N(\phi) = \frac{N_0 \sigma}{2} e^{-\sigma|\phi|} . \tag{9}$$

As Landahl has shown, the results obtained with such a function are very similar to those obtained with a normal distribution.

Equation (9) gives

$$\text{For } \phi > 0 \quad N(\phi) = N_+(\phi) = \frac{N_0 \sigma}{2} e^{-\sigma\phi} ; \tag{10}$$

$$\text{For } \phi < 0 \quad N(\phi) = N_-(\phi) = \frac{N_0 \sigma}{2} e^{\sigma\phi}. \tag{11}$$

The function $P_1(\phi)$ is determined by the distribution function of the fluctuation at the connection activated by ε_1 and ε_2, (Landahl, 1938). Assuming this distribution function to be

$$p(\xi) = \frac{k}{2} e^{-k|\xi|}, \tag{12}$$

we have (Landahl, 1937; Rashevsky, 1948)

$$\text{For } \phi > 0 \qquad P_1 = 1 - \tfrac{1}{2} e^{-k\phi}; \tag{13}$$

$$\text{For } \phi < 0 \qquad P_1 = \tfrac{1}{2} e^{k\phi}. \tag{14}$$

When the situation described by equation (8) takes place then, as we have said, we must substitute $\phi + \psi$ for ϕ. Instead of (13) and (14) we then obtain, for $\psi > 0$:

$$\text{For } \phi > -\psi \qquad P_1 = 1 - \tfrac{1}{2} e^{-k(\phi+\psi)}; \tag{15}$$

$$\text{For } \phi < -\psi \qquad P_1 = \tfrac{1}{2} e^{k(\phi+\psi)}. \tag{16}$$

We shall consider ϕ, the initial value of the excitation difference, as a constant characterizing each individual. Thus P_1 is a function of the initial value ϕ and of the added value ψ.

Equation (8) may be written

$$\frac{d\psi}{dt} = A \int_{-\infty}^{+\infty} [x(\phi) - y(\phi)]\, d\phi - a\psi. \tag{17}$$

But, according to (2) and (3), we now have

$$x(\phi) = P_1(\phi, \psi) N(\phi); \qquad y(\phi) = N(\phi)[1 - P_1(\phi, \psi)]. \tag{18}$$

Hence

$$x(\phi) - y(\phi) = N(\phi)[2P_1(\phi, \psi) - 1]. \tag{19}$$

Introducing now (10), (11), (15) and (16) into the integral in (17) we find

$$\begin{aligned} \int_{-\infty}^{+\infty} [x(\phi) - y(\phi)]\, d\phi &= \int_{-\infty}^{+\infty} N(\phi)\, [2P_1(\phi, \psi) - 1]\, d\phi \\ &= \frac{N_0 \sigma}{2} \left\{ \int_{-\infty}^{-\psi} e^{\sigma\phi}\, (e^{k(\phi+\psi)} - 1)\, d\phi + \int_{-\psi}^{0} e^{\sigma\phi}\, [1 - e^{-k(\phi+\psi)}]\, d\phi \right. \\ &\quad \left. + \int_{0}^{\infty} e^{-\sigma\phi}\, [1 - e^{-k(\phi+\psi)}]\, d\phi \right\}. \end{aligned} \tag{20}$$

Evaluating the integrals in (20) and substituting them into (17), we find, after rearrangements,

$$\frac{d\psi}{dt} = AN_0 \left\{ 1 + \frac{k^2}{\sigma^2 - k^2} e^{-\sigma\psi} - \frac{\sigma^2}{\sigma^2 - k^2} e^{-k\psi} \right\} - a\psi. \qquad (21)$$

We shall now investigate the expression in braces. There are three cases:

Case I. $k > \sigma$.

For $\psi = 0$ the expression in braces is zero. For $\psi = \infty$ it is equal to 1. The second term is negative and decreases to zero more slowly

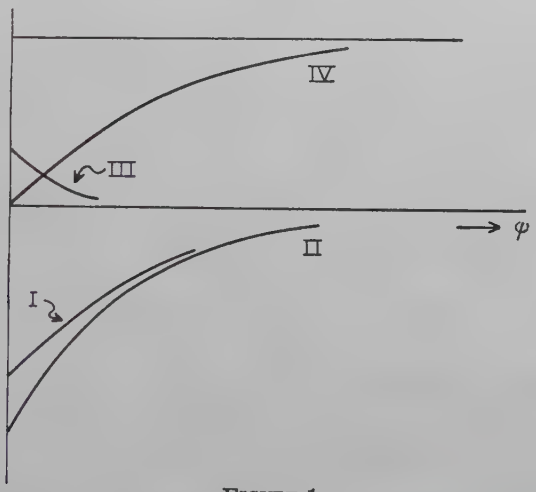

FIGURE 1

than the third, which is positive (Fig. 1, curves II and III). The first derivative is equal to

$$-\frac{k^2\sigma}{\sigma^2 - k^2} e^{-\sigma\psi} + \frac{k\sigma^2}{\sigma^2 - k^2} e^{-k\psi}, \qquad (22)$$

and is positive for $\psi = 0$, being equal to $k\sigma/(\sigma + k)$.

The second derivative is equal to

$$\frac{k^2\sigma^2}{\sigma^2 - k^2} (e^{-\sigma\psi} - e^{-k\psi})$$

and is everywhere negative, so that there is no inflection point.

The sum of the second and third terms in the braces is thus shown by curve I in Figure 1. The whole expression in braces is represented by curve IV of Figure 1.

Case II. $k < \sigma$.

Now the second term is positive and decreases more rapidly than the third, which is negative (the curves II and III in Figure 1 merely interchange their parts). The first derivative is again positive for $\psi = 0$. The sum of the two exponentials is thus again a monotonically increasing curve, starting at -1 for $\psi = 0$ and tending asymptotically to zero (Fig. 1, curve I). The total expression in braces is represented by curve IV of Figure 1, and is again the same as in Case I.

Case III. $k = \phi$.

Put

$$k = \sigma + \Delta, \tag{23}$$

where Δ is a small quantity, tending to zero. Preserving only linear terms in Δ, we have

$$\sigma^2 - k^2 = -2\sigma\Delta. \tag{24}$$

Substituting (23) and (24) into the expression in braces of (21) we find for that expression, after rearrangements:

$$1 + \frac{\sigma e^{-\Delta\psi} - \sigma - 2\Delta}{2\Delta} e^{-\sigma\psi}. \tag{25}$$

As Δ tends to zero, expression (25) tends to

$$1 - \left(1 + \frac{\sigma\psi}{2}\right) e^{-\sigma\psi}. \tag{26}$$

It is again represented by a curve starting at zero and increasing monotonically, tending asymptotically to 1.

Denoting the expression in braces in (21) by $F(\psi)$, we see that $d\psi/dt = 0$ when

$$F(\psi) = \frac{a}{AN_0}\psi. \tag{27}$$

If for $\psi = 0$ the derivative of $AN_0F(\psi) > a$, or because of (22), if

$$\frac{a}{AN_0} < \frac{k\sigma}{\sigma + k}, \tag{28}$$

then equation (27) has one positive root ψ^*, as is seen from Figure 2. The configuration which corresponds to that root is stable, because for

$\psi < \psi^*$ we have $d\psi^*/dt > 0$, while for $\psi > \psi^*$, $d\psi/dt < 0$.

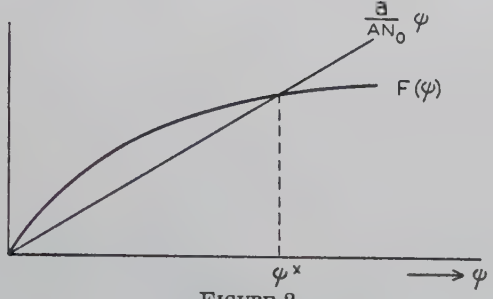

FIGURE 2

If, however, inequality (27) is not satisfied, then the configuration $X = Y$ is stable. Though a slight excess of X makes the term $A(X - Y)$ in (8) non-vanishing, it remains less than $a\psi$.

To determine the values of X and Y at the stable point ψ^*, we must express X in terms of ψ. The other variable, Y, is given by

$$Y = N_0 - X. \tag{29}$$

We have

$$X = \int_{-\infty}^{+\infty} x(\phi)\, d\phi. \tag{30}$$

Introducing (10), (11), (13), (14), (15) and (16) into the first equation (18), and introducing the latter into (30) we find

$$X = \frac{N_0 \sigma}{2}\left\{ \tfrac{1}{2} \int_{-\infty}^{-\psi} e^{\sigma\phi}\, e^{k(\phi+\psi)} d\phi + \int_{-\psi}^{0} e^{\sigma\phi}[\, 1 - \tfrac{1}{2}\, e^{-k(\phi+\psi)}]\, d\phi \right. \tag{31}$$
$$\left. + \int_{0}^{\infty} e^{-\sigma\phi}\, [1 - \tfrac{1}{2}\, e^{-k(\phi+\psi)}]\, d\phi \right\}.$$

Evaluating the integrals, we find

$$X = \frac{N_0 \sigma}{2}\left\{ \frac{2}{\sigma} + \frac{\sigma}{\sigma^2 - k^2}\, e^{-\sigma\psi} - \frac{1}{\sigma}\, e^{-\sigma\psi} - \frac{\sigma}{\sigma^2 - k^2}\, e^{-k\psi} \right\}. \tag{32}$$

Putting $\psi = \psi^*$ into (32), we obtain the value of X at that point. The problem thus reduces to the solution of the transcendental equation (27). The following method of successive approximation may be suggested. Equation (27) is of the form

$$1 + \alpha\, e^{-\sigma\psi} - \beta\, e^{-k\psi} = \gamma\, \psi, \tag{33}$$

with

$$\alpha = \frac{k^2}{\sigma^2 - k^2}; \quad \beta = \frac{\sigma^2}{\sigma^2 - k^2}; \quad \gamma = \frac{a}{AN_0}. \tag{34}$$

As a zeroth approximation we take the point of intersection of the line $\gamma\,\psi$ with the asymptote, that is we put (Fig. 3)

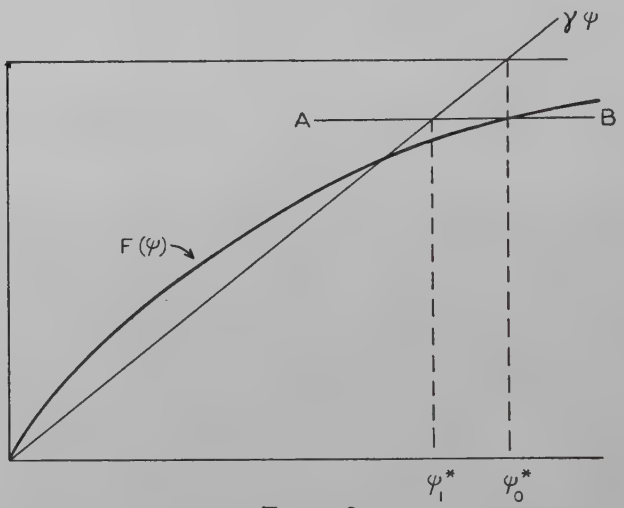

FIGURE 3

$$\psi_0^* = \frac{1}{\gamma}. \tag{35}$$

Then we introduce this value into $F(\psi)$, and take as the first approximation the point of intersection of the straight line $\gamma\,\psi$ with the horizontal line $F(\psi_0^*)$ (Line AB, Fig. 3). This gives

$$\gamma\,\psi = F(\psi_0^*) \tag{36}$$

or

$$\psi_1^* = \frac{F(\psi_0^*)}{\gamma}. \tag{37}$$

Writing $F(\psi)$ explicitly, we have

$$\psi_1^* = \frac{1}{\gamma}(1 + \alpha^{-\sigma/\gamma} - \beta\, e^{-k/\gamma}). \tag{38}$$

For the case in which X is large, this approximation should be fairly sufficient. We may, however, proceed further by putting

$$\psi_2^* = \frac{F(\psi_1^*)}{\gamma}, \tag{39}$$

and in general

$$\psi_{n+1}^* = \frac{F(\psi_n^*)}{\gamma}. \tag{40}$$

The larger N_0, the smaller γ, and therefore, as seen from Figure 3, the larger ψ_0^*. From equation (32) we see that X increases with ψ.

We thus obtain the following result: A society in which the tendencies toward two mutually exclusive activities are distributed amongst the individuals according to a symmetric distribution function will, as a result of imitation of behavior, show either one or the other of the two behaviors predominantly in certain cases. For constant neurobiological parameters, A and a, the predominance will be greater, the larger the total population N_0. For sufficiently large values of N_0 practically all of the society will exhibit the same behavior. The choice, however, between the two mutually exclusive behaviors is determined by pure accident.

The importance of a possible generalization of this result to n different behaviors is obvious. This shall be discussed in a subsequent paper.

Consider now the case in which the function $N(\phi)$ is not symmetric. Let the asymmetry favor the negative values of ϕ, in other words favor behavior R_2. One possible way of obtaining such a distribution would be to put, instead of (10) and (11):

$$\text{For } \phi > 0 \quad N(\phi) = N_+(\phi) = \frac{N_0 \sigma_1 \sigma_2}{\sigma_1 + \sigma_2} e^{-\sigma_2 \phi}; \tag{41}$$

$$\text{For } \phi < 0 \quad N(\phi) = N_-(\phi) = \frac{N_0 \sigma_1 \sigma_2}{\sigma_1 + \sigma_2} e^{\sigma_1 \phi}; \tag{42}$$

with

$$\sigma_1 < \sigma_2. \tag{43}$$

Now introducing (41), (42), (15) and (16) into (17) we find after elaborate calculations:

$$\frac{d\psi}{dt} = AN_0 \left\{ 1 + \frac{2k^2 \sigma_2}{(\sigma_1 + \sigma_2)(\sigma_1^2 - k^2)} e^{-\sigma_1 \psi} - \frac{\sigma_1 \sigma_2}{(\sigma_1 - k)(\sigma_2 + k)} e^{-k\psi} \right\} - a\psi. \tag{44}$$

Denoting the expression in braces by $F_1(\psi)$ now, let us investigate that function. Let us compare it with the function $F(\psi)$ for the case in which $\sigma = \sigma_1$ in the latter.

First consider the case in which

$$\sigma_2 > \sigma_1 > k\,. \tag{45}$$

A comparison of the expressions in braces in equations (21) and (44) shows that the second, positive, term in $F_1(\psi)$ is greater than the corresponding term in $F(\psi)$. We have

$$\frac{2k^2\,\sigma_2}{(\sigma_1+\sigma_2)\,(\sigma_1{}^2-k^2)}-\frac{k^2}{\sigma_1{}^2-k^2}=\frac{k^2}{\sigma_1+\sigma_2}\,\frac{\sigma_2-\sigma_1}{\sigma_1{}^2-k^2}>0. \tag{46}$$

Similarly we find that the third, negative, term of $F_1(\psi)$ is greater in *absolute value* than the corresponding terms of $F(\psi)$. We have

$$\frac{\sigma_1\,\sigma_2}{(\sigma_1-k)\,(\sigma_2+k)}-\frac{\sigma_1{}^2}{\sigma_1{}^2-k^2}=\frac{\sigma_1\,k}{\sigma_2+k}\,\frac{\sigma_2-\sigma_1}{\sigma_1{}^2-k^2}>0. \tag{47}$$

But the difference between the absolute values of the positive terms is less than the difference between the absolute values of the negative terms. Those two differences are given respectively by the right-hand sides of equations (46) and (47). Since, because of (45),

$$k^2<\sigma_1\,k;\qquad \sigma_1+\sigma_2>\sigma_2+k\,, \tag{48}$$

therefore

$$\frac{k^2}{\sigma_1+\sigma_2}<\frac{\sigma_1\,k}{\sigma_2+k}, \tag{49}$$

and hence the right-hand side of equation (46) is less than the right-hand side of (47).

Thus the negative term in $F_1(\psi)$ exceeds the negative term in $F(\psi)$ more than the positive term of $F_1(\psi)$ exceeds the positive term of $F(\psi)$. Therefore

$$F_1(\psi)<F(\psi). \tag{50}$$

When

$$\sigma_2 > k > \sigma_1\,, \tag{51}$$

we have

$$\frac{\sigma_1\,k}{k+\sigma_2}<\frac{k^2}{\sigma_1+\sigma_2}. \tag{52}$$

Remembering that the second terms now are negative and the

third term positive, and that inequalities (46) and (47) are now reversed, we see that the deficiency of the negative term in $F_1(\psi)$ over that of $F(\psi)$ is greater than the deficiency of the positive term. Hence again we have inequality (50).

The case $k > \sigma_2 > \sigma_1$ leads to the same result. Inequality (50) holds also for $\psi = 0$. Hence

$$F_1(0) < 0. \tag{53}$$

Only for $\psi = \infty$ do both $F(\psi)$ and $F_1(\psi)$ tend to the same asymptotic value 1.

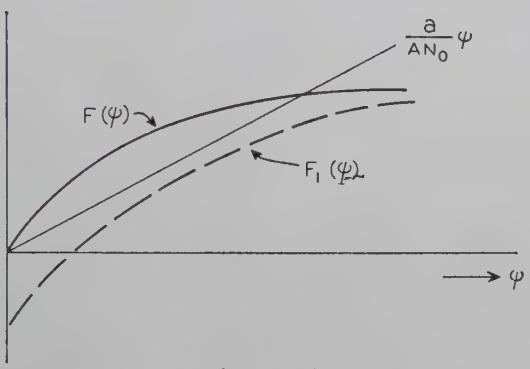

FIGURE 4

The relations between $F(\psi)$, $F_1(\psi)$ and $\frac{a}{AN_0}\psi$ are shown graphically in Figure 4. If σ_1 become sufficiently small, that is the asymmetry favoring negative values of ϕ becomes sufficiently large, other parameters being kept constant, then $F_1(\psi)$ will vary as represented by the broken line. It will not intersect the line $(a/AN_0)\psi$, and a stable configuration in which $X > Y$ will not exist. It is, however, readily seen that a stable configuration with $Y > X$ will exist in that case.

Let $N(\phi)$ be originally symmetric, $(\sigma_1 = \sigma_2 = \sigma)$, and let the stable configuration with a strong preponderance of X, (R_1) be accidentally established. Then let, due to a biological variation of the social group, $N(\phi)$ become asymmetric in favor of $R_2(\sigma_1 < \sigma_2)$. In that case as σ_2 increases it will eventually reach the threshold, at which the broken curve in Figure 4 will just become tangent to the straight line. At this moment $d\psi/dt$ will become negative and the configuration will "jump" over into one for which R_2 prevails and $Y >> X$.

Another way to introduce an asymmetric distribution function $N(\phi)$ is to put

$$N(\phi) = \frac{N_0 \sigma}{2} e^{-k|\phi_0 - \phi|}. \tag{54}$$

The function $N(\phi)$ is now symmetric with respect to $\phi = \phi_0$, but not with respect to zero. Whereas in the case of the function (9) the average value $\bar{\phi}$ of ϕ is zero, in the case of (54) it is a function of ϕ_0. By the same procedure as above we may derive X and Y as a function of $\bar{\phi}$ or of ϕ_0.

From (18) we see that $x(\phi)$ is also a function of the parameter ψ, and should be written $x(\phi, \psi)$. Since ϕ is independent of t, we have

$$\frac{dx(\phi, \psi)}{dt} = \frac{\partial x(\phi, \psi)}{\partial \psi} \frac{d\psi}{dt}. \tag{55}$$

Substituting for $d\psi/dt$ its expression from equation (8) we find

$$\frac{dx(\phi, \psi)}{dt} = A \frac{\partial x(\phi, \psi)}{\partial \psi} (X - Y) - a \frac{\partial x(\phi, \psi)}{\partial \psi} \psi. \tag{56}$$

Integrating with respect to ϕ between $-\infty$ and $+\infty$ we find, because of (30):

$$\frac{dX}{dt} = A(X - Y) \int_{-\infty}^{+\infty} \frac{\partial x(\phi, \psi)}{\partial \psi} d\phi - a\psi \int_{-\infty}^{+\infty} \frac{\partial x(\phi, \psi)}{\partial \psi} d\phi. \tag{57}$$

We shall now compute the quantity

$$Z = \int_{-\infty}^{+\infty} \frac{\partial x(\phi, \psi)}{\partial \psi} d\phi. \tag{58}$$

Introducing (15) and (16) into (18), we find

$$x(\phi, \psi) = N(\phi)[1 - \tfrac{1}{2} e^{-k(\phi+\psi)}] \qquad \text{for } \phi > -\psi; \tag{59}$$

$$x(\phi, \psi) = \tfrac{1}{2} N(\phi) e^{k(\phi+\psi)} \qquad \text{for } \phi < -\psi. \tag{60}$$

Differentiating we have:

$$\frac{\partial x(\phi, \psi)}{\partial \psi} = \frac{k}{2} N(\phi) e^{-k(\phi+\psi)} \qquad \text{for } \phi > -\psi; \tag{61}$$

$$\frac{\partial x(\phi, \psi)}{\partial \psi} = \frac{k}{2} N(\phi) e^{k(\phi+\psi)} \qquad \text{for } \phi < -\psi. \tag{62}$$

Comparing (61) and (62) with (59) and (60) we see that

$$\text{For } \phi > -\psi \qquad \frac{\partial x(\phi, \psi)}{\partial \psi} = kN(\phi) - kx(\phi, \psi); \tag{63}$$

$$\text{For } \phi < -\psi \qquad \frac{\partial x(\phi, \psi)}{\partial \psi} = kx(\phi, \psi). \tag{64}$$

Hence

$$Z = k \int_{-\infty}^{-\psi} x(\phi, \psi)\, d\phi + k \int_{-\psi}^{+\infty} N(\phi)\, d\phi - k \int_{-\psi}^{+\infty} x(\phi, \psi)\, d\phi. \tag{65}$$

Introducing now for $N(\phi)$ the expressions (10) and (11), using (18), (15) and (16) and evaluating the integrals we find:

$$Z = \frac{N_0 k \sigma}{4} \left\{ \frac{2\sigma}{\sigma^2 - k^2} e^{-k\psi} - \frac{2k}{\sigma^2 - k^2} e^{-\sigma\psi} \right\}. \tag{66}$$

Eliminating ψ from equations (32) and (66), we would obtain Z as a function of X. Unfortunately it is impossible to eliminate ψ because both expressions are transcendental. We may however perform this for the two limiting cases, namely, when $\sigma << k$, and when $\sigma >> k$.

When $\sigma << k$ we have from (66) and (32):

$$Z = \frac{N_0 k^2 \sigma}{2(k^2 - \sigma^2)} e^{-\sigma\psi}; \tag{67}$$

$$X = \frac{N_0 \sigma}{2} \left\{ \frac{2}{\sigma} + \left(\frac{\sigma}{\sigma^2 - k^2} - \frac{1}{\sigma} \right) e^{-\sigma\psi} \right\} = N_0 + \frac{N_0 k^2}{2(\sigma^2 - k^2)} e^{-\sigma\psi}. \tag{68}$$

Hence

$$Z = \sigma(N_0 - X). \tag{69}$$

For $\sigma >> k$ we find in a similar way

$$Z = k(N_0 - X). \tag{70}$$

Denoting by $1/\kappa$ an appropriate average of $1/k$ and $1/\sigma$, for instance

$$\frac{1}{\kappa} = \frac{1}{2}\left(\frac{1}{k} + \frac{1}{\sigma} \right), \tag{71}$$

we have approximately, in general,

$$Z = \kappa(N_0 - X). \tag{72}$$

When $\sigma << k$, we have from (32)

$$\psi = \frac{1}{\sigma} \log \frac{N_0}{2(N_0 - X)}. \tag{73}$$

When $\sigma >> k$, we have

$$\psi = \frac{1}{k} \log \frac{N_0}{2(N_0 - X)}. \tag{74}$$

Hence approximately we have, in general,

$$\psi = \frac{1}{\kappa} \log \frac{N_0}{2(N_0 - X)}. \tag{75}$$

Introducing (72) and (75) into (57) we obtain

$$\frac{dX}{dt} = A\kappa(N_0 - X)(X - Y) - a(N_0 - X) \log \frac{N_0}{2(N_0 - X)}. \tag{76}$$

Because of the assumption of $\psi > 0$ in (15) and (16) this equation as well as all preceding ones hold only in the range between $X = \frac{1}{2} N_0$ and $X = N_0$.

For $X < \frac{1}{2} N_0$; $Y > \frac{1}{2}$ we have, because of the symmetry of $N(\phi)$

$$\frac{dY}{dt} = A\kappa(N_0 - Y)(Y - X) - a(N_0 - Y) \log \frac{N_0}{2(N_0 - Y)}, \tag{77}$$

which, because of $Y = N_0 - X$, gives

$$\frac{dX}{dt} = A\kappa X(X - Y) + aX \log \frac{N_0}{2X}. \tag{78}$$

We now may generalize our results by considering not merely the frequency of reactions R_1 and R_2, but also their intensities.

For the two categories case (Landahl, 1938) considered here, it is seen that for a constant value of $\phi (> 0)$ the intensity of R_1 is proportional to ϕ, so that

$$R_1 = \alpha \phi. \tag{79}$$

A fluctuation $-\xi$ changes ϕ to $\phi - \xi$, and therefore we have

$$R_1 = \alpha(\phi - \xi). \tag{80}$$

To have any reaction R_2 at all, we must have

$$\phi - \xi > 0 \qquad \text{or} \qquad \xi < \phi. \tag{81}$$

Hence if $p(\xi)$ is the fluctuation function [equation (12)], we have for the average intensity $\bar{R}_1$ of R_1:

$$\bar{R}_1 = \frac{\alpha \int_{-\infty}^{\phi} (\phi - \xi) p(\xi) d\xi}{\int_{-\infty}^{\phi} p(\xi) d\xi}. \tag{82}$$

Substituting for $p(\xi)$ its expression as given by (12), remembering that

$$\text{for } \xi < 0 \qquad p(\xi) = \frac{k}{2} e^{k\xi}; \tag{83}$$

$$\text{for } \xi > 0 \qquad p(\xi) = \frac{k}{2} e^{-k\xi}; \tag{84}$$

and evaluating the integrals, we find

$$\text{For } \phi > 0 \qquad \bar{R}_1 = \frac{2\alpha\phi + \frac{\alpha}{k} e^{-k\phi}}{2 - e^{-k\phi}}. \tag{85}$$

$$\text{For } \phi < 0 \qquad \bar{R}_1 = \frac{\alpha}{k}. \tag{86}$$

The average intensity of R_1 increases with ϕ for positive values of ϕ, and for very large ϕ we have

$$\bar{R}_1 = \alpha\phi. \tag{87}$$

For $\phi < 0$, when R_1 is always "accidental" its average intensity is constant and equal to that for $\phi = 0$, as obtained from (85).

Equation (82) may be written:

$$\bar{R}_1 = \frac{\alpha\phi \int_{-\infty}^{\phi} p(\xi)\, d\xi - \alpha \int_{-\infty}^{\phi} \xi p(\xi)\, d\xi}{\int_{-\infty}^{\phi} p(\xi)\, d\xi} = \alpha(\phi - \bar{\xi}), \tag{88}$$

where $\bar{\xi}$ denotes the average fluctuation in the interval $-\infty$ to ϕ. Computing $\bar{\xi}$, we find

$$\text{For } \phi > 0 \qquad \bar{\xi} = -\frac{\left(\phi + \frac{1}{k}\right) e^{-k\phi}}{2 - e^{-k\phi}}. \tag{89}$$

$$\text{For } \phi < 0 \qquad \bar{\xi} = \phi - \frac{1}{k}. \tag{90}$$

Substituting (89) or (90) into (88) we again find (85) or (86).

Now we may consider that the stimulus which increases ψ, according to equation (8), is not $X - Y$, but the difference of the total intensities R_1 and R_2, that is

$$\int_{-\infty}^{+\infty} [\bar{R}_1(\phi + \psi)\, x(\phi + \psi) - \bar{R}_2(\phi + \psi)\, y(\phi + \psi)]\, d\psi. \tag{91}$$

As is readily seen, this expression is a function of ψ only.

Denote by n the average number of acts of either R_1 or R_2 done by an individual per unit time. If the average age of an individual in the society is T, then the average number of acts performed by the individual during his lifetime is nT. If the probability P_1 for some individuals is less than $1/nT$, those individuals will on the average never perform a reaction R_1 in their lifetimes. Similarly, if $P_2 < 1/nT$, such individuals never do, for all practical purposes, perform R_2. Let Δ_1 be the root of the equation

$$P_1(\phi + \psi^*) = \frac{1}{nT} \tag{92}$$

when solved for ϕ while Δ_2 is the root of

$$P_2(\phi + \psi^*) = \frac{1}{nT} \tag{93}$$

when solved for ϕ. Then we may say that all individuals with $\phi < \Delta_1$ will never perform R_1, while all individuals with $\phi > \Delta_2$ will never perform R_2.

We may now break the range of integration in (91) into three intervals

$$-\infty, \Delta_1; \qquad \Delta_1, \Delta_2; \qquad \Delta_2, +\infty. \tag{94}$$

Denote by $\bar{a}_0$ and $\bar{a}$ appropriate average values of $\bar{R}_1(\phi + \psi)$ in the intervals Δ_2, $+\infty$ and Δ_1, Δ_2 correspondingly. Similarly denote by $\bar{c}_0$ and $\bar{c}$ appropriate averages of $\bar{R}_2(\phi + \psi)$ in the intervals $-\infty$, Δ_1 and Δ_1, Δ_2 correspondingly. Putting

$$\begin{aligned} X_0 &= \int_{\Delta_2}^{+\infty} x(\phi + \psi)\, d\phi; \qquad Y_0 = \int_{-\infty}^{\Delta_1} y(\phi + \psi)\, d\phi; \\ X &= \int_{\Delta_1}^{\Delta_2} x(\phi + \psi)\, d\phi; \qquad Y = \int_{\Delta_1}^{\Delta_2} y(\phi + \psi)\, d\phi, \end{aligned} \tag{95}$$

and using the mean value theorem, we see that the integral (91) becomes

$$\bar{a}_0 X_0 + \bar{a} X - \bar{c}_0 Y_0 - \bar{c} Y \,. \tag{96}$$

Instead of equations (76) and (78) we now obtain:
For $X > \frac{1}{2} N_0$

$$\frac{dX}{dt} = A \kappa (N_0 - X)(\bar{a}_0 X_0 + \bar{a} X - \bar{c}_0 Y_0 - \bar{c} Y) - a (N_0 - X) \log \frac{N_0}{2(N_0 - X)}; \tag{97}$$

For $X < \frac{1}{2} N_0$

$$\frac{dX}{dt} A \kappa X (\bar{a}_0 X_0 + a X - c_0 Y_0 - c Y) + a X \log \frac{N_0}{2X}. \tag{98}$$

If a is so small that the log term may be neglected, and if, *as a very crude approximation,* we substitute in both (97) and (98) an appropriate constant time average for $(N - X)$ and X, then both (97) and (98) reduce formally to equation (2) of chapter iii of our book (Rashevsky, 1948a). As has been remarked in a previous paper (Rashevsky, 1949), the coefficients a_0, c_0, a and c are still functions of time, and appropriate averages of them should be used.

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OUTLINE OF A PROBABILISTIC APPROACH TO ANIMAL SOCIOLOGY: II

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Under certain assumptions concerning the probabilities of "mutations," i.e. changes of structure of bird societies, it is shown that the probability distribution for all possible structures of a society of N individuals approaches a limit independent of the initial probability distribution. A formula for the limiting distribution is derived.

In a previous paper (Rapoport, 1949), hereafter referred to as I, we examined the possible "structures" of bird societies as determined by the distribution of peck rights among the individuals of a flock. It was shown that on the basis of certain assumptions concerning the probabilities of the outcomes of encounters between individuals, it was possible to compute the probability of establishing each of the various structures. It was assumed in I that as a result of the first encounter between a pair of individuals, the peck right relation was established for this pair once for all.

In the present paper more general assumptions will be made. A peck right relation between two individuals will be considered undisputed during a finite time only. Eventually another encounter may occur, as a result of which the peck right relation may be reversed.

Consider a society of N individuals. Associated with N there are n possible structures as described in I. Let us suppose that from time to time encounters take place between pairs of individuals. The result of each encounter may be either the preservation of the old peck right relation between the two individuals or its reversal. If the peck right relation is preserved, then certainly the structure of the society is also preserved. On the other hand, if the peck right relation is reversed, the structure may be changed, or it may not. For example, the structure S_1: (2, 1, 0) of the three-individual society is diagramatically represented as follows (Cf. I):

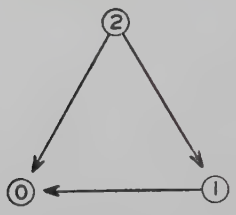

FIGURE 1

A reversal of peck right between individuals 2 and 0 changes the structure to S_2: (1, 1, 1), thus:

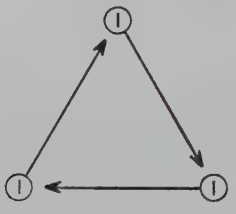

FIGURE 2

But the reversal of peck right between 2 and 1 results again in the structure (2, 1, 0) with the individuals simply relabeled:

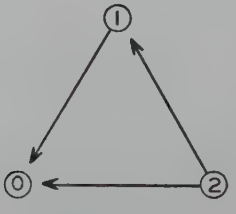

FIGURE 3

We shall refer to changes in structure as "structure mutations" or simply as "mutations" and will denote the mutation $S_i \rightarrow S_j$ by S_{ij}. The probability of the occurrence of S_{ij} will be denoted by a_{ij}.

In general, not every mutation S_{ij} can be accomplished by a single reversal of peck right. The corresponding a_{ij} will then be zero. Otherwise $a_{ij} (i \neq j)$ will depend on the probability of an encounter between a pair of individuals which may result in S_{ij} and on the probability of the victory going to the "submissive" individual. However, in estimating the ultimate fate of the society (the limiting probability distribution of its possible structures), one may use the para-

meters a_{ij} directly and compute the limiting distribution in terms of these. The computation of the a_{ij} in terms of the probabilities of encounters and reversals is a separate problem. We shall first state the problem of determining the limiting distribution in terms of the a_{ij}.

The Matrix (a_{ij}).

Let $S_i(t)$ be the probability of occurrence of the structure S_i at the time t. Take as a unit of time the average interval between encounters. Then

$$\begin{aligned}
S_1(t) &= a_{11}S_1(t-1) + a_{21}S_2(t-1) + \cdots a_{n1}S_n(t-1) \\
S_2(t) &= a_{12}S_1(t-1) + a_{22}S_2(t-1) + \cdots a_{n2}S_n(t-1) \\
&\cdots\cdots \\
S_n(t) &= a_{1n}S_1(t-1) + \cdots\cdots\cdots a_{nn}S_n(t-1).
\end{aligned} \tag{1}$$

Note that the S_{ii} are the "identity mutations," thus, a_{ii} is the probability of the preservation of the structure S_i. We denote the matrix of the probabilities by (a_{ij}). The attention of the reader is called to the fact that the subscript notation is the reverse of the conventional one, a_{ij} being the element of the ith *column* and the jth row. We have chosen this departure from convention in order to keep the suggestion that a_{ij} stands for the probability of S_i mutating to S_j.

If $S(t)$ is the vector $\{S_1(t), S_2(t), \cdots S_n(t)\}$, equation (1) may be written in vector-matrix notation thus:

$$S(t) = (a_{ij})S(t-1). \tag{2}$$

Hence by iteration,

$$S(t) = (a_{ij})^t S(0), \tag{3}$$

and

$$S(\infty) = \operatorname*{Lim}_{t=\infty} (a_{ij})^t S(0): \tag{4}$$

If the limit in equation (4) exists, then the vector $S(\infty)$ will represent the distribution of the structures S_i after a long time, that is, if a great many societies are allowed to exist for a sufficiently long time, the components of $S(\infty)$, $S_i(\infty)$ represent the expected fractions of the total number of societies to have the structure S_i.

Let us examine the properties of the matrix (a_{ij}). As was shown in I, each structure is obtainable from the "simple chain" by a finite number of peck right reversals. Therefore the simple chain is so obtainable from any structure, and hence any structure is obtainable from any other by a finite number of reversals. Thus, any change of structure $S_i \rightarrow S_j$, even though it may not be possible by a single mutation S_{ij}, can take place by a finite number of steps,

$$S_i \rightarrow S_k \rightarrow \cdots S_j .$$

This is stated in Property 4 below. We shall also assume that any structure *may* be preserved in an encounter. This is equivalent to the assumption that the diagonal elements of (a_{ij}) are not zero. Finally, since the elements of each column exhaust all possible mutations of a structure, all the column sums must be unity. We summarize these properties as follows.

Property 1: $0 \leqq a_{ij} \leqq 1$.

Property 2: $\sum_j a_{ij} = 1$.

Property 3: $\prod_i a_{ii} \neq 0$.

Property 4: If $a_{ij} = 0$, there exist elements a_{ik}, a_{kl}, a_{lm}, $\cdots$ a_{mj}, such that the product $a_{ik}a_{kl} \cdots a_{mj} \neq 0$.

Our principle result is embodied in the following

Theorem. *There exists a matrix* $(\alpha_{ij}) = \operatorname{Lim}_{t=\infty} (a_{ij})^t$, *such that the columns of* (α_{ij}) *are all identical. The vector represented by any of these columns is the limiting distribution vector* $S(\infty)$, *and it is independent of the initial distribution* $S(0)$.

Proof of the Limiting Distribution Theorem.

We shall establish a number of lemmas, which will enable us to prove the limiting distribution theorem.

Lemma 1. *The elements* $a_{ij}^{(t)}$ *of the matrix* $(a_{ij})^t$ *satisfy Property* 1 *and Property* 2 *of* (a_{ij}).

We shall prove an induction on t. Assume that the elements $a_{ij}^{(t-1)}$ satisfy both properties.

But

$$
\begin{aligned}
a_{i1}^{(t)} &= a_{11}^{(t-1)}\, a_{i1} + a_{21}^{(t-1)}\, a_{i2} + \cdots a_{n1}^{(t-1)} a_{in} \\
a_{i2}^{(t)} &= a_{12}^{(t-1)}\, a_{i1} + a_{22}^{(t-1)}\, a_{i2} + \cdots a_{n2}^{(t-1)} a_{in} \\
&\cdots\cdots \\
a_{in}^{(t)} &= a_{1n}^{(t-1)}\, a_{i1} + \cdots\cdots\cdots a_{nn}^{(t-1)} a_{in}\,.
\end{aligned} \tag{5}
$$

Since $0 \leqq a_{ij}$ and $0 \leqq a_{ij}^{(t-1)}$, obviously $0 \leqq a_{ij}^{(t)}$. To obtain $\sum_j a_{ij} = 1$, we add the equations (5) and get

$$
\begin{aligned}
\sum_j a_{ij}^{(t)} &= a_{i1} \sum_j a_{1j}^{(t-1)} + a_{i2} \sum_j a_{2j}^{(t-1)} \\
&\quad + \cdots a_{in} \sum_j a_{nj}^{(t-1)} = \sum_j a_{ij} = 1.
\end{aligned} \tag{6}
$$

This establishes the induction and proves the lemma.

Lemma 2. *For all* t, Max. $\{a_{1h}^{(t)}, \cdots a_{nh}^{(t)}\} \leqq$ Max. $\{a_{1h}^{(t-1)}, \cdots a_{nh}^{(t-1)}\}$ *and* Min. $\{a_{1h}^{(t)}, \cdots a_{nh}^{(t)}\} \geqq$ Min. $\{a_{1h}^{(t-1)}, \cdots a_{nh}^{(t-1)}\}$, $h = (1, 2 \cdots n)$.

Proof. To fix ideas, consider the elements of the first row of the matrix $(a_{ij})^t$. We have

$$
\begin{aligned}
a_{11}^{(t)} &= a_{11}^{(t-1)}\, a_{11} + a_{21}^{(t-1)}\, a_{12} + \cdots a_{n1}^{(t-1)}\, a_{1n} \\
a_{21}^{(t)} &= a_{11}^{(t-1)}\, a_{21} + a_{21}^{(t-1)}\, a_{22} + \cdots a_{n1}^{(t-1)}\, a_{2n} \\
&\cdots\cdots \\
a_{n1}^{(t)} &= a_{11}^{(t-1)}\, a_{n1} + \cdots\cdots\cdots a_{n1}^{(t-1)}\, a_{nn}\,.
\end{aligned} \tag{7}
$$

Let $a_{k1}^{(t-1)} =$ Max. $a_{i1}^{(t-1)}$. Then, by (7)

$$
a_{11}^{(t)} \leqq a_{k1}^{(t-1)} \sum_j a_{1j} = a_{k1}^{(t-1)}, \tag{8}
$$

since $\sum_j a_{1j} = 1$. Similarly $a_{21}^{(t)} \leqq a_{k1}^{(t-1)}$, etc., for all $a_{i1}^{(t)}$ $(i = 1, 2 \cdots n)$, and, in particular, Max. $a_{i1}^{(t)} \leqq a_{k1}^{(t-1)} =$ Max. $a_{i1}^{(t-1)}$.

The proof for the minimum element is exactly analogous.

Lemma 3. *The maximum (minimum) element of each row of the matrix* $(a_{ij})^t$ *tends to a limit as* t *increases without bound.*

This follows from the fact that the sequences

$$\text{Max.}\{a_{1i}^{(t)}, a_{2i}^{(t)} \cdots a_{ni}^{(t)}\} \text{ and Min.}\{a_{1i}^{(t)}, a_{2i}^{(t)} \cdots a_{ni}^{(t)}\}$$

are both monotone and bounded by zero below and by unity above.

Lemma 4. *There exists an integer* r *such that* $a_{ij}^{(t)} \neq 0$ *for* $t > r$ $(i, j = 1, 2, \cdots n)$.

The lemma implies that sufficiently high powers of (a_{ij}) have no zero elements.

Proof. To begin with, if $a_{ij} \neq 0$, then $a_{ij}^{(t)} \neq 0$. We show this by induction, assuming $a_{ij}^{(t-1)} \neq 0$. Then

$$a_{ij}^{(t)} = a_{1j}^{(t-1)} a_{i1} + a_{2j}^{(t-1)} a_{i2} + \cdots a_{ij}^{(t-1)} a_{ii} + \cdots a_{nj}^{(t-1)} a_{in}. \tag{9}$$

But $a_{ij}^{(t-1)} \neq 0$ by the hypothesis of the induction, and $a_{ii} \neq 0$ by Property 3. Furthermore, all the other terms on the right side of (9) are non-negative by Lemma 1. Therefore $a_{ij} \neq 0$.

Suppose now that $a_{ij} = 0$. Then by Property 4, there exist elements a_{ik}, a_{kl}, a_{lm}, $\cdots$ a_{mj}, all positive. In conventional notation, these elements would be denoted by a_{jm}, a_{ml}, a_{lk}, $\cdots$ a_{ki}. Now $a_{jl}^{(2)} = \sum_h a_{jh} a_{hl} \neq 0$, since $a_{jm} a_{ml} \neq 0$. Similarly $a_{jk}^{(3)} = \sum_h a_{jh}^{(2)} a_{hk} \neq 0$, since $a_{jl}^{(2)} a_{lk} \neq 0$. Proceeding in this way, we obtain $a_{ji}^{(r)} \neq 0$ for some integer r. But this is $a_{ij}^{(r)}$ in our notation. It follows by the proof of the first part of the lemma that all higher orders $a_{ij}^{(t)}$ are not zero. This proves the lemma.

Lemma 5. *Let* $\alpha_j = \lim_{t=\infty} \text{Max.}\{a_{1j}^{(t)}, a_{2j}^{(t)} \cdots a_{nj}^{(t)}\}$. *Then for every* $\varepsilon > 0$, *there exists an integer* t_1, *such that for* $t > t_1$, $|\alpha_j - a_{ij}^{(t)}| < \varepsilon$ $(i = 1, 2 \cdots n)$, *that is, all the elements of the* jth *row of* $(a_{ij})^t$ *tend to* α_j *as a limit.*

Proof. Again let us fix our attention on the first row. Let s be such that for $t > s$ Max. $\{a_{i1}^{(t)}\} - \alpha_1 < \varepsilon_1$, where $\varepsilon_1 = \varepsilon \cdot$ Min. $a_{ij}^{(r)}/(1 +$ Min. $a_{ij}^{(r)})$ as shown in Lemma 3. Let r be such that for $t \geqq r$, $a_{ij}^{(t)} > 0$, as shown in Lemma 4. Choose $t = r + s$. Then $(a_{ij})^t = (a_{ij})^s (a_{ij})^r$. Let $a_{k1}^{(s)} =$ Max. $\{a_{11}^{(s)}, a_{21}^{(s)} \cdots a_{n1}^{(s)}\}$ and $a_{m1}^{(t)} =$ Max. $\{a_{11}^{(t)}, a_{21}^{(t)} \cdots a_{n1}^{(t)}\}$. Then

$$a_{k1}^{(s)} = a_{k1}^{(s)} a_{m1}^{(r)} + a_{k1}^{(s)} a_{m2}^{(r)} + \cdots a_{k1}^{(s)} a_{mn}^{(r)}, \tag{10}$$

since $\sum_j a_{mj} = 1$ by Lemma 1. On the other hand

$$a_{m1}^{(t)} = a_{11}^{(s)} a_{m1}^{(r)} + a_{21}^{(s)} a_{m2}^{(r)} + \cdots a_{n1}^{(s)} a_{mn}^{(r)}. \tag{11}$$

By Lemma 2, $\alpha_j \leqq a_{m1}^{(t)} \leqq a_{k1}^{(s)}$, so that by our hypothesis on s, $a_{k1}^{(s)} - a_{m1}^{(t)} < \varepsilon_1$. Subtracting equation (11) from (10), we get

$$a_{m1}^{(r)}\,(a_{k1}^{(s)} - a_{11}^{(s)}) + a_{m2}^{(r)}\,(a_{k1}^{(s)} - a_{21}^{(s)}) + \cdots a_{mn}^{(r)}\,(a_{k1}^{(s)} - a_{n1}^{(s)}) < \varepsilon_1 . \tag{12}$$

We have proved the first part of our theorem, namely that $(a_{ij})^t$ tends to a limiting matrix with equal columns. For sufficiently large t, therefore, $(a_{ij})^t$ may be written as $(\alpha_{ij}) + (\varepsilon_{ij})$ where

$$\alpha_{ij} = \begin{Vmatrix} \alpha_1 \alpha_1 \cdots \alpha_1 \\ \alpha_2 \alpha_2 \cdots \\ \cdot \\ \cdot \\ \cdot \\ \alpha_n \cdots \alpha_n \end{Vmatrix} \tag{13}$$

and $|\text{Max } \varepsilon_{ij}|$ is arbitrarily small. Now if S is an arbitrary vector with non-negative components, whose sum is unity, the product $(\alpha_{ij})S$ is independent of S, being the vector $\{\alpha\} \equiv \{\alpha_1, \alpha_2 \cdots \alpha_n\}$. On the other hand $(\varepsilon_{ij})S$ gives the vector $\{\sum_i \varepsilon_{i1}S_1, \sum_i \varepsilon_{i2}S_2, \cdots \sum_i \varepsilon_{in}S_n\}$, each of whose components is less than $|\text{Max. } \varepsilon_{ij}|$ in absolute value and hence arbitrarily small. But $(a_{ij})^t S = (\alpha_{ij})S + (\varepsilon_{ij})S = \{\alpha\} + \text{infinitesimal}$. Therefore $\lim_{t=\infty} (a_{ij})^t S = \{\alpha\}$ and is independent of S. Our theorem is thus proved.

The Calculation of the Limiting Distribution.

We have shown that for every mutation probability matrix having properties 1 - 4, there exists uniquely a limiting distribution vector. This vector is invariant under the linear transformation (a_{ij}) and therefore satisfies the equations

$$(a_{ij})S = S; \tag{14}$$

$$\sum_i S_i = 1. \tag{15}$$

The solution of (14) reduces to the solution of $n - 1$ simultaneous linear equations. The existence and the uniqueness of the solution is guaranteed by the limiting distribution theorem. We have, in view of (15)

$$
\begin{aligned}
S_1 &= a_{11}S_1 + a_{21}S_2 + \cdots a_{n1}(1 - \sum_{i=1}^{n-1} S_i) \\
S_2 &= a_{12}S_1 + a_{22}S_2 + \cdots a_{n2}(1 - \sum_{i=1}^{n-1} S_i) \qquad (16) \\
&\cdot \\
&\cdot \\
&\cdot \\
S_{n-1} &= a_{1(n-1)}S_1 + a_{2(n-1)}S_2 + \cdots a_{n(n-1)}(1 - \sum_{i=1}^{n-1} S_i),
\end{aligned}
$$

and, after proper transpositions,

$$
\begin{aligned}
&S_1[1 - (a_{11} - a_{n1})] + S_2(a_{n1} - a_{21}) + \cdots \\
&\qquad S_{n-1}(a_{n1} - a_{(n-1)1}) = a_{n1} \\
&S_2(a_{n2} - a_{12}) + S_2[1 - a_{22} - a_{n2})] + \cdots \\
&\qquad S_{n-1}(a_{n2} - a_{(n-1)2}) = a_{n2} \qquad (17) \\
&\cdot \\
&\cdot \\
&\cdot \\
&\cdot \\
&S_{(n-1)}(a_{n(n-1)} - a_{1(n-1)}) + \cdots \\
&S_{(n-1)}[1 - (a_{n(n-1)} - a_{(n-1)(n-1)})] = a_{n(n-1)}.
\end{aligned}
$$

Denote by (b_{ij}) the $(n-1)$-rowed matrix obtained by deleting the nth row and nth column of the matrix, $[I - (a_{ij} - a_{nj})]$, where I is the identity matrix and denote by $(b_{ij})^{(i)}$ the matrix obtained by replacing the ith column of (b_{ij}) by the vector $\{a_{n1}, a_{n2}, \cdots a_{n(n-1)}\}$. Then by Cramer's rule, the components of the limiting distribution vector are given by

$$
S_i = \frac{|(b_{ij})^{(i)}|}{|(b_{ij})|}, \quad (i = 1, 2 \cdots n). \qquad (18)
$$

Example: *Society of Three Individuals.*

In case $N = 3$, $n = 2$, and the system (16) reduces to a single equation,

$$
S_1 = a_{11}S_1 + a_{21}(1 - S_1) \qquad (19)
$$

whose solution is

$$
S_1 = a_{21}/(1 - a_{11} + a_{21}), \qquad (20)
$$

then obviously

$$S_2 = 1 - S_1 = (1 - a_{11})/(1 - a_{11} + a_{21}).$$

We can now make assumptions concerning the probabilities of encounters and victories, and on the basis of these assumptions compute a_{11} and a_{21}. If an encounter between any pair of individuals is equally likely and the probability of victory does not depend on the peck right relation existing before the encounter, that is, it is $\frac{1}{2}$ for each individual, the calculation of the a_{ij} is quite simple. Since the mutation S_{21} can occur as a result of any encounter (Cf. Fig. 2), provided the peck right relation is reversed, we have $a_{21} = \frac{1}{2}$. On the other hand, S_1 is preserved in 5 out of 6 possible results of encounters as can be seen from Figure 1. Hence $a_{11} = 5/6$, and

$$S_1 = \frac{1/2}{1 - 5/6 + 1/2} = 3/4; \quad S_2 = 1/4. \tag{21}$$

Note that this distribution is also the initial distribution for $N = 3$ shown in I to result from random initial victories.

The "mutation" method, however, enables us to introduce biases which may depend on inherent properties of individuals and on their social rank. Thus the probability of an encounter between individuals of widely different social rank may be taken to be smaller than that between individuals of nearly equal rank. Likewise the probability of victory of a dominant individual may be taken to be greater than that of the submissive individual, etc. Hysteresis phenomena may likewise be introduced, that is the dependence of victories on the number of past victories enjoyed by the individual, etc. Some of these complications will be discussed in later papers.

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NEURAL MECHANISMS FOR HEDONISTIC BEHAVIOR

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Some neural mechanisms are described which interpret neurobiophysically the determination of the behavior of an individual by the maximizing of his satisfaction, or pleasure.

The concept of the satisfaction function has proved to be very useful in the theory of social behavior (Rashevsky, 1948a; Rapoport, 1947a,b,c; Rapoport and Shimbel, 1947). The postulate that an individual behaves in such a way as to maximize his satisfaction function, or the sum of the satisfaction functions of all individuals, has been introduced in a purely formal manner without any neurobiophysical interpretation. An attempt at such an interpretation has been made by H. D. Landahl (1948). However, Landahl's theory has an unpleasant feature, namely, that the behavior of an individual is determined not exactly by the maximum of certain neurobiophysical functions, but only approximately. In the present paper we shall suggest two mechanisms which avoid this difficulty.

The first mechanism assumes that hedonistic behavior, that is behavior characterized by the maximalization of one's own satisfaction function, is not innate, but learned.

Consider the case studied by H. D. Landahl [1941; Rashevsky, 1948b (chap. xli)] in which an individual learns to choose one "correct" stimulus out of a total of N stimuli. In Landahl's theory the "correct" stimulus is characterized by the circumstance that the reaction to it produces an additional central excitation which reinforces that reaction. A "wrong" stimulus is characterized by the fact that a reaction to it results in a central inhibition which weakens the reaction.

Let us now modify that situation somewhat by considering that every reaction to any one of the N stimuli results in a reinforcing excitation. The degree of reinforcement is, however, assumed to be different for the different stimuli. The stimulus which is reinforced the most strongly will prevail, gradually inhibiting the other stimuli. Thus the organism *learns* to choose the stimulus which results in the

greatest reinforcement. Considering the degree of reinforcement as the measure of subjectively felt satisfaction, or pleasure, we find that the organism learns to choose the stimulus which results in the greatest pleasure.

The rate of this learning can be obtained directly from Landahl's equation by making the constant β [Rashevsky, 1948, p. 473, equation (11)] negative.

Now let us consider that the same reaction of different intensity produces different environmental changes in such a way that the change produced by a certain optimal intensity results in a maximum pleasure. Since stimuli of different intensities result in differently localized central excitations (Rashevsky, 1948b, chap. xxxiii), the reactions to different intensities are produced *via* different central regions. A choice between different intensities of the same reaction is thus reduced to the choice between spatially different central stimuli. The case is reduced to the preceding one. Again the organism learns to use that intensity of a reaction which gives maximum satisfaction.

We may finally consider the case in which a constant stimulus produces a constant reaction, resulting in an increase of something which itself acts as a rewarding stimulus. This something may have a maximum value as a function of the duration of the reaction.

Let the organism cut off the reaction at different times t_1, t_2 $\cdots$ t_n, among which is included the optimal time t^*. To each of these times there corresponds an intensity, or quantity, S_1, S_2 $\cdots$ S_n of the "something" that results in some satisfaction. Thus the organism develops a series of conditioned reflexes, in each of which a given intensity S_i results in the cutting off of the reaction. If all those conditioned pathways are cross-inhibited, then the strongest will prevail. But that strongest conditioned pathway will be the one corresponding to S^*, the strongest conditioned stimulus.

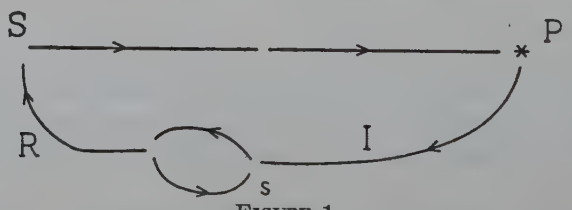

FIGURE 1

Now let us consider a different mechanism which does not involve learning directly. Let the stimulus S excite the center P, which we shall call "pleasure center" (Fig. 1). Let the intensity of excitation of P have a maximum for a certain intensity of S.

Let the pleasure center P excite a pathway, I, which leads to the connection s, and which is characterized by the following relation between its parameters (Rashevsky, 1948b, p. 444).

$$B_j < A_j; \quad b_j < a_j; \quad \frac{A_j}{a_j} = \frac{B_j}{b_j}. \tag{1}$$

At the connection s there is a self-circuited neuroelement which produces a cumulative increase of excitation, resulting in the reaction R. The latter in its turn again produces the stimulus S.

Under those conditions any sufficiently sudden increase in the excitation of P will result in a temporary excitation of the pathway, and therefore in a reinforcement at s (Rashevsky, 1948b, p. 444). On the other hand, any sufficiently sudden decrease of the excitation of P will result in a temporary inhibition of the pathway, and therefore in a weakening of the cumulative excitation at s.

Let the organism produce a reaction R resulting in a certain S. This will produce a certain P, and as a result R will be reinforced. Thus a stronger S will be produced the second time, which will again be reinforced as long as an increase in S results in an increase of excitation in P. But when the excitation of P reaches a maximum, a further increase in R, or S, will result in a decrease of the excitation at P, and therefore in a decrease of reinforcement at s. Thus R and S will be reinforcing each other only until the excitation at P has reached a maximum. An accidental increase of R beyond the value R_{max} will result in a decrease of excitation at P, and therefore in a weakening of R.

The mechanism requires sufficiently sudden changes in the intensity of R, or S. It is, however, likely that it may be generalized to continuous changes.

According to the picture suggested here, an organism acts altruistically, that is tries to maximize the satisfaction of others, if the satisfaction of others acts as a pleasant stimulus on that individual. From this point of view altruism is just another form of egoism.

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ANALYSES OF SPONTANEOUS AND INDUCED MUTATIONS OF THE TOBACCO MOSAIC VIRUS

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Various types of analyses of the existing data on spontaneous and X-ray induced mutations of the tobacco mosaic virus to the aucuba variant are discussed on the basis of the known phytopathological, biochemical and biophysical facts. It is concluded that if virus protein is the X-ray absorbing medium through which the mutation is induced 3% of the total virus protein would be involved in this primary process. If nucleic acid were the medium through which the ionizing energy must be absorbed in order to induce the mutation, 25% of the amount of this acid existing in the virus would be needed. The analysis shows also the complete insignificance of the naturally occurring ionizing radiations for the process of spontaneous mutation of the virus.

Since the rediscovery of Mendel's idea early in the current century the geneticists accepted as their fundamental concepts the corpuscular structure of the hereditary material in the cell and the random and discrete character of the primary processes which confer to the nucleus a hereditary change. During the same time physicists discovered the corpuscular structure of radiation energy and the random character of its interaction with the irradiated atoms. The discrete and haphazard character of directly observable events induced by the absorption of radiation energy has been revealed in a convincing manner by the cloud chamber, the electronic counter and the photographic emulsion. With less direct evidence but perhaps with equal firmness the concepts of corpuscular structure, of a random type of action and of a discrete number of essential primary events became basic ideas in the study of hereditary changes. It is therefore perhaps not chance that the applications of radiations in genetics have been so rich in results; since the concepts of randomness and discreteness are fundamental to both radiation physics and genetics.

Whatever the form of the energy inducing a mutation is and whatever may be the mechanism of the mutation the experimental facts suggest that:

(i) in order to induce a mutation a certain amount of energy must be absorbed by a certain volume (v) in the cell;

(ii) the absorption of this amount of energy by that volume consists of a number of particular random events (E).

It is generally believed that the number of such events which are sufficient to induce a mutation is small, mostly one for mutations occurring in a single gene, and one or two for changes involving a whole chromosome (cf. Timoféeff-Ressovsky, 1937, pp. 122–123; Fano and Demerec, 1944; Lea, 1947a, 1947b). However examples are available in which a larger number of primary events is necessary for the induction of a detectable mutation. Recessives in polyploids belong fundamentally to this case; in the field of unicellular organisms cases are known in which effects essentially equivalent to lethals appear as a cumulative action of several events (see e.g. Lacassagne, 1930; Glocker, Langendorff and Reuss, 1933; Schreiber, 1934). Consequently we will not put a priori any restriction on the number of events (E), since this should be obtainable from an analysis of the experimental data.

Events (E) physically identical with those inducing a mutation occur in the whole organism and throughout the entire sample under experimentation but only few of them occur in the volumes (v). We will indicate with p the *probability that an event* (*E*) *occurs in the volume* (*v*) *of a given biological unit* (a sperm, a cell, a whole organism) *if it occurs in the experimental material containing that unit once per each* μ^3 *in average.* The probability p for the induction of a hereditary change depends on the geometric structure and on the chemical composition of the volume (v) and of the whole experimental object.

We will indicate with N_D the number of events (E) produced per μ^3 of the experimental material by the amount of energy D. We will assume that each of these events, if it occurs in the volume (v), has an immediate effect, although its detection may be delayed. To take into account the spontaneous mutation we have to keep in mind that when the administration of the experimental amount of energy D starts, some of those effects may be already existing in some units of our sample. We will indicate with N_S the number of ionizations that would have to be produced per μ^3 of the sample, in order to produce exactly the effects existing in it, if the sample were completely free from such effects. With respect to the type of energy actually used in the experiment and with reference to the phenotypic character under consideration, N_S is some sort of *energy equivalent of the genetic status of the sample.* We will assume that the sample is a statistically correct representative of the population out of which it is taken and that this population is in equilibrium with respect to

the mutation considered, so that there is always a constant probability for a spontaneous mutation. We will indicate with $P(N_S + N_D)$ the probability of inducing a mutation with an amount of *administered* energy equal to D, consequently the probability of a spontaneous mutation will be indicated by $P(N_S)$. The term $N_S + N_D$ expresses here the cooperative action of the experimentally administered and of the spontaneously absorbed energies. In analyzing the induction of mutations by X-rays, we assume that the events (E) consist of ionizations. Approximately 32.5 eV are required to produce a pair of ions in biological material, so that in a round figure two ionizations per μ^3 are produced by each roentgen of absorbed energy; consequently if D is measured in roentgen, we may take as a very crude approximation: $N_D \approx 2D$.

Two situations at least are possible a priori: (i) the appearance of a mutation may require the occurrence of an exact number n of events (E) in (v); (ii) the genotype or at least its phenotypic expression may be stable to such an extent that events (E) occurring in (v) beyond a certain number n do not produce any detectable change within experimental limits. In the first case the probability of induction of a mutation is:

$$p_n = \binom{N}{n} p^n q^{N-n} \quad \text{with } q = 1 - p ,$$

in the second case it is:

$$P_n = \sum_{i=n}^{\infty} p_i = 1 - \sum_{i=0}^{n-1} p_i , \tag{1}$$

where N is the number of events (E), i.e. of ionizations, per μ^3 of the sample. If N is very large there are two types of asymptotic relations (cf. e.g. Castelnuovo, 1925, chap. v; Uspensky, 1937, pp. 129–136; Cramér, 1946, pp. 198–206):

$$p_n = (2\pi Npq)^{-1/2} \exp\left[-(Np - n)^2/(2Npq)\right]; \tag{2}$$

$$P_n = \int_{-\infty}^{u} \exp(-x^2)\, dx/\sqrt{\pi} \tag{3}$$

with $u = (Np - n)/(2Npq)^{1/2}$, (theorems of De Moivre, Laplace and Tchebychef) and

$$p_n = e^{-w} w^n/n! \quad \text{with } w = Np , \tag{4}$$

$$P_n = 1 - e^{-w} \sum_{i=0}^{n-1} w^i/i! \qquad (5)$$
$$= \int_0^w e^{-x}\, x^{n-1}\, dx/(n-1)\,! = \gamma(w, n)$$

(Poisson distributions). This last integral is the incomplete gamma function for which the symbol γ is here used. The validity of formulas (2) and (3) requires in general that p and q be large, whereas in formulas (4) and (5), it is sufficient that p or q be small. In all radiogenetical applications of probability it has been found that p is extremely small; for this reason we will use the formulas (4)—(5).

If more than one event (E) is necessary for the induction of a detectable mutation the question arises whether the effect of *each* such event is hereditary or not. We will assume that it is, in the same way as a mutation in a single recessive gene is hereditary. However this question enters into our analysis only insofar as a cellular division may occur between two events (E) in (v). This may happen very infrequently in mutations induced by radiations, because of the very short duration of experimentation. The question may be important though in interpreting spontaneous mutations.

We proceed now to a more concrete interpretation of the probability p. Let us consider for instance the expression (5). If we take the number of ionizations produced per μ^3 as the measure of the energy absorbed, the mean energy absorbed per mutation is n/p. This is a known result from the theory of the *cumulative Poisson distribution* [cf. e.g. Opatowski, 1946, formula (2)]. If a mutation requires n ionizations in the volume v, it requires n/v ionizations per μ^3; consequently $n/p = n/v$ and $p = v$. Therefore if the energy producing a mutation is measured as the number of ion pairs that it produces per μ^3 of the irradiated material, *the probability* p *is the volume* v *in* μ^3 *in which this energy must be absorbed to produce the mutation.* This conclusion implies the assumption that each event (E) occurring in (v) produces its effect. If a certain probability of effectiveness is attached to the events (E) the interpretation of p must be modified accordingly (cf. e.g. Timoféeff-Ressovsky and Zimmer, 1947, pp. 97–99).

We analyze here the spontaneous and X-ray induced *mutations of the tobacco mosaic virus from ordinary type to aucuba type* (Gowen, 1941). Because the reproductive mechanism of a virus consists of a simple division, it is reasonable to assume, at first at least, that any hereditary change in the virus is transmitted to both of its off-

springs. We assume also that the hereditary changes with which we deal do not affect the rate of reproduction of the virus. Then the proportions of viruses of a sample containing certain hereditary properties are independent of the process of division, consequently this will not appear in the mathematical expressions of those proportions.

The viruses are detected by counting the number of lesions that they produce in plants. For viruses used in solution, the number of lesions is proportional to the number of viruses only over a small range of their concentration. However since in the experiments of J. W. Gowen a single type of technique has been consistently used, we assume, at first, that his data are not affected by a concentration effect (cf. Bawden, 1943; Doerr, 1939; Stanley, 1938). It will be seen later that this assumption is not likely to involve a serious error.

In using the experimental results we have to keep in mind that the X-rays have at least two effects on the virus: mutation and inactivation, and that reverse mutations occur also. Since no experimental technique is known which would prevent a simultaneous occurrence of these effects, several types of analysis are possible.

(i) In view of the fact that the aucuba mosaic viruses, which are formed in the course of experimentation from the tobacco mosaic viruses, are subject—after their formation—to a much smaller dosage of X-rays, in average, than the original tobacco mosaic viruses, we may neglect the reverse and other possible mutations as well as the inactivations of those newly formed aucuba mosaic viruses, in a first approximation at least. However we will take into account the fact that a tobacco mosaic virus must survive a dose D in order to be mutated by it. The data for the inactivation will be taken from the results of J. W. Gowen (1940) which give for the probability of a tobacco mosaic virus surviving as such a dose of D roentgen of 1.5 Å wave length the following relation:

$$S(N_D) = \exp(-415 \times 10^{-8} D), \tag{6}$$

which is valid for the range of D corresponding to the mutation data (see Fig. 1). Exponential survival curve is given also by A. Marshak and W. N. Takahashi (1942), although differences in experimental conditions make their coefficient of D different from that of J. W. Gowen. We take $P(N_S + N_D)$ as the probability of the mutation of a tobacco mosaic virus under the assumption that it survives as such the administered dose D of X-rays. Then we have to put:

$$P(N_S + N_D) = A/[TS(N_D)], \tag{7}$$

where T is the number of the tobacco mosaic lesions obtained from an unirradiated sample and A is the number of the aucuba mosaic le-

sions obtained after the irradiation of the sample; $S(N_D)$ is calculated here for each D from (6). To correlate the probability of mutation with the energy which produces it we calculate $P(N_D)$ from the following equation

$$P(N_S + N_D) = P(N_S) + [1 - P(N_S)]\, P(N_D). \tag{8}$$

This is a probabilistic expression of the two ways in which a virus may mutate; either spontaneously or in consequence of the energy D. From (8) we obtain

$$\begin{aligned} P(N_D) &= [P(N_D + N_S) - P(N_S)]/[1 - P(N_S)] \\ &\approx P(N_D + N_S) - P(N_S), \end{aligned} \tag{9}$$

since $P(N_S)$ is negligible with respect to unity. In the present case it is 0.00079. Applying formula (5) we obtain two equations for the unknown v and n:

$$\begin{aligned} &\gamma(vN_S, n) = P(N_S); \\ &\gamma(vN_S + vN_D, n) = P(N_S + N_D); \end{aligned} \tag{10}$$

the right-hand sides being known from observation.

The lower part of Figure 1 on the right represents the probability of mutation $P(N_D)$ as a function of the energy in roentgen to which the mutation is due. The values represented by dots have been calculated by means of the formulae (7)—(9) using the experimental data of J. W. Gowen. In order to change the roentgen of the figure into N_D, i.e. into number of ionizations per μ^3, the abscissae must be multiplied by a suitable factor. If it is assumed that the genetically effective ionization occurs in the *whole virus* this factor may be taken as 1.45; this is a value given by D. E. Lea (1947a, p. 8) for dried virus at 1.5 Å, which are the experimental conditions of the analyzed data. The application of the theory to these data has been carried out in the following manner: First of all from the equation of spontaneous mutations

$$\gamma(vN_S, n) = 0.00079 \tag{11}$$

the dependence of vN_S on n has been numerically tabulated. These values of vN_S have been substituted into equation (10) and from the equations thus obtained, a numerical relation between v and n has been obtained for each pair of values of P and N_D calculated from the experimental data. If for a certain value of n the fit were perfect, the corresponding values of v calculated for all the pairs of (P, N_D) would be the same. However such a perfect case does not

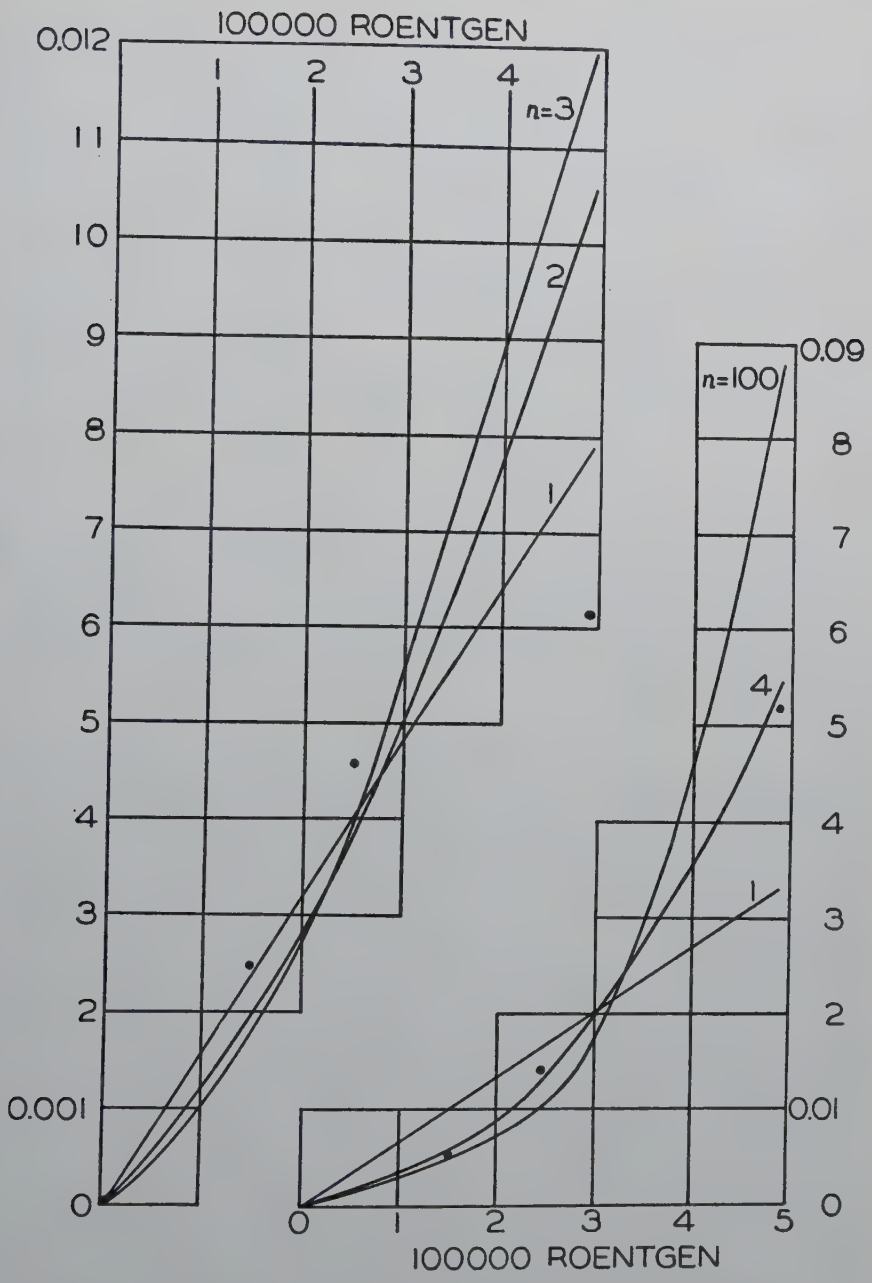

FIGURE 1. *Probability* $P(N_D)$ *of mutation of the tobacco mosaic virus to aucuba against the energy* D *in roentgen which produces this mutation.*
Theoretical curves and points computed from the experimental data.

VALUES OBTAINED FROM THE THEORETICAL FORMULAE

Theory I (lower part of the figure to the right)

n	$\bar{v}$ in μ^3	$\sigma/\bar{v}$ in %
1	4.65×10^{-8}	45.7
2	3.80×10^{-7}	14.3
3	8.97×10^{-7}	4.5
4	1.42×10^{-6}	2.0
5	1.88×10^{-6}	2.7
6	2.43×10^{-6}	5.3
7	2.94×10^{-6}	7.2
100	2.20×10^{-5}	12.0

Theory II (upper part of the figure to the left)

n	$\bar{v}$ in μ^3	$\sigma/\bar{v}$ in %
1	1.09×10^{-8}	15.7
2	1.67×10^{-7}	21.8
3	4.24×10^{-7}	24.4

$\bar{v}$ is calculated on the basis of an average absorption coefficient of the whole virus which is practically equal to the absorption coefficient of the protein component of the virus. The calculations imply that each ionization in (v) is effective. If it is assumed that ions appear in clusters of 3 in average (Jordan, 1938) so that each effective event (E) consists not of one but of three ionizations, the above values of $\bar{v}$ must be multiplied by 3.

present itself in general. Consequently the standard deviation of all the calculated values of v from their arithmetic mean $\bar{v}$ has been computed. The smallest standard deviation is obtained for $n = 4$ with $\sigma/\bar{v} = 0.02$. Figure 1 and the table show that the fit is very good and that it would not be so with another value of n. The theory gives in this way a volume v of 1.42×10^{-6} μ^3, which is practically identical with the effective absorption volume of a vital dominant gene in the sex chromosome of Drosophila (1.1×10^{-6} μ^3 according to J. W. Gowen, 1934; experiments with approximately 1.5 Å X-rays). It is also about of the order of magnitude of the volume for the sex linked lethals in Drosophila: 10^{-5} μ^3 according to U. Fano (1942). J. W. Gowen (1940) calculated a volume of 7.5×10^{-6} μ^3, whose ionization produces the *inactivation* of the tobacco mosaic virus. A. Marshak and W. N. Takahashi (1942) give a size of this volume between 4.6×10^{-6} μ^3 and 42×10^{-6} μ^3. The fact that the volume for inactivation is several times larger than for mutation agrees with the fact that it takes much more energy to mutate a sample of viruses than to inactivate it.

A very large number of papers has been written on the size of the tobacco mosaic virus. Methods of ultrafiltration (Bawden and

Pirie, 1937; Smith and MacClement, 1938), electron microscopy (Kausche, 1939; Kausche, Pfankuch and Ruska, 1939; Anderson and Stanley, 1941; Stanley and Anderson, 1941; Stanley, 1943; Williams and Wyckoff, 1945), X-ray diffraction (Bawden, Pirie, Bernal and Fankuchen, 1936; Bernal and Fankuchen, 1941), measurements of sedimentation, diffusion constants and viscosity (Bechhold and Schlesinger, 1933; Wyckoff, Biscoe and Stanley, 1937; Frampton and Neurath, 1938; Lauffer, 1938a, b; Mehl, 1938; Neurath and Saum, 1938) have been all used to find some information on the shape and the size of this virus directly or through its molecular weight determination (Bernal and Fankuchen, 1937; Bernal, 1938; Stanley, 1938, 1939, 1941; Stanley and Loring, 1938; Frampton, 1939; Lauffer and Stanley, 1939; McFarlane, 1939; Cohen and Stanley, 1942; Markham, Smith and Lea, 1942; Lauffer, 1944; Harrow, 1946, pp. 80–84; Lea, 1947a, p. 136). The extreme results of most of these determinations differ from each other by a factor of few units. The differences are due, in part at least, to experimental techniques which may cause such effects as breakages of the virus by mechanical stress or by thermal agitation (cf. Sigurgeirsson and Stanley, 1947). Reasons have been also suggested to doubt whether the size of the tobacco mosaic virus can be considered a constant (Pirie, 1945, p. 15; 1946), since there is some evidence that the virus consists of basic particles which arrange themselves in a linear fashion, the number of such particles of the virus and consequently its length being dependent on the environment (Bawden and Pirie, 1945). However the distribution of this length has a pronounced and extremely sharp maximum at 280 mμ (Sigurgeirsson and Stanley, 1947; Oster and Stanley, 1946; Rawlins, Roberts and Utech, 1946). This is also the minimum length at which the virus shows its infective activity. It is therefore justified to consider it as the length of the virus (Stanley et al). The average value accepted today by most workers as the volume of the tobacco mosaic virus lies between about 4×10^{-5} to about 5×10^{-5} μ^3. If the above quoted length of 280 mμ together with a cross-sectional diameter of 15 mμ according to W. M. Stanley et al is accepted, the volume comes out to 4.96×10^{-5} μ^3. It is for this reason that we will assume in the following calculations the round figure of 5×10^{-5} μ^3 as the volume of the virus. The fact that in fresh unaltered plant juice the virus may appear in aggregates of a much larger size (Williams and Steere, 1949) has no bearing here.

It has been recognized that a mutation of the virus is due neither to a splitting of its original volume nor to a polymerization (cf. e.g. Gowen, 1945). The problem arises then to identify within the virus the volume (v) responsible for its mutation. J. D. Bernal and I. Fan-

kuchen (1941) found through an extensive X-ray investigation that the protein of the tobacco mosaic virus consists of many *hexagonal unit cells* with a base of 87Å side length and 68 Å height. This gives for the volume of each such cell 1.34×10^{-6} μ^3, which is *very close to our theoretical volume of* $v = 1.42 \times 10^{-6}$ μ^3. According to J. D. Bernal and I. Fankuchen the unit cells are arranged along the length of the virus with their hexagonal bases adjacent to each other. This type of structure is confirmed by recent high magnification electron micrographs (Markham, 1947; Wyckoff, 1947). If the "mutation volume" (v) is actually one of the hexagonal cell units the present theory would indicate that these units, although geometrically identical, have different biological functions because only a particular one of these units would be responsible for the mutation of the virus. Such a situation is not surprising in principle, since one can imagine physiochemical differences between the end and the intermediate cells.

The calculation of the volume within which the primary process of mutation takes place gives us the possibility to consider a controversial question. E. Pfankuch, G. A. Kausche and H. Stubbe suggested in 1940 that mutation of the tobacco mosaic virus under the action of X- and γ-rays may be due to changes in its nucleic acid content. Their suggestion was based on solubility determinations and on other physicochemical measurements, but mainly on electrophoresis which showed that at least 90% of the protein of the tobacco mosaic virus and of its variant strain were identical. The tobacco mosaic virus is known to be a nucleoprotein and its nucleic acid group to be particulary efficient in responding to the action of X-rays because of its much higher average atomic number due to a relatively high content of phosphorus. (The mass absorption coefficient for X-rays is proportional to more than the 4th power of the atomic number. Nucleic acid of the tobacco mosaic virus contains about 9% of $_{15}$P whereas the element of highest atomic number in the protein is $_{16}$S whose content however is only 0.24%; see Loring, 1939; Stanley, 1939.)

On the contrary, W. M. Stanley (1941), C. A. Knight and M. A. Lauffer (Knight and Stanley, 1941; Stanley and Knight, 1941; Knight and Lauffer, 1942) concluded after their analyses that the differences between strains of tobacco mosaic virus are located probably in amino acids and that there is little evidence at least for their being in the nucleic acid. The question is of interest because it has been conjectured that the nucleic acid plays an important role in the induction of mutations in general. In fact, the dependence of the absorption coefficient of the nucleic acid on the wave length of ultra-

violet and the dependence of the genetic effect on the same wave length show a partial but quite close correlation (Catcheside, 1948, p. 358). Even the lethal spectrum of certain unicellular organisms has been found to coincide with the absorption spectrum of the nucleic acid in the ultraviolet region (Jordan, 1939, p. 479).

Assuming for a moment that the whole volume (v) which is the site of the primary mutational events consists entirely of nucleic acid the size of (v) could be calculated in the following manner. The X-ray mass absorption coefficient of this acid due to photoelectric effect and to transfer of energy to recoil electrons is 12.46 gr^{-1} for the wave length of 1.5 Å used by J. W. Gowen. This value has been calculated according to the method indicated by D. E. Lea (1947a, p. 349), i.e. from the experimental values of S. J. M. Allen for the total mass absorption coefficients (Compton and Allison, 1946, p. 802) the absorption coefficient due to scattered radiation has been subtracted. The latter has been calculated from a table of D. E. Lea (1947a, p. 348) based on Klein-Nishina formula (cf. Mayneord, 1940). The chemical composition used for these calculations was H = 4.16%, C = 33%, N = 15.1%, P = 9.13%, 0 = 38.61% (by difference). These are averages calculated from the data of H. S. Loring (1939). On the basis of the calculated absorption coefficient of 12.46 gr^{-1} and of the value of 1.6 for the density of the nucleic acid of the tobacco mosaic virus (Stanley and Loring, 1938) it is found that 1 roentgen produces 3.74 ionizations in 1 μ^3 of the nucleic acid. Consequently if that part of the administered X-ray energy which is responsible for the mutation were absorbed entirely by the nucleic acid, the volume v would be:

$$1.42 \times 1.45 \times 10^{-6}/3.74 = 5.5 \times 10^{-7}\ \mu^3,$$

because in applying formula (10) to a set of experimental data, a change of the number of ionizations per μ^3 per roentgen implies a change in the same proportion of N_D and consequently a change of v in the inverse proportion.

Since the nucleic acid amounts to about 5.5% in weight of the virus (Cohen and Stanley, 1942; also Schramm and Dannenberg, 1944) and the density of the latter is 1.3 (Stanley and Loring, 1938; Lauffer, 1944) the volume of the nucleic acid existing in the virus is, if the size of the latter is taken as $5 \times 10^{-5}\ \mu^3$

$$5 \times 10^{-5} \times 0.055 \times 1.3/1.6 = 2.23 \times 10^{-6}\ \mu^3,$$

which is about 4 times larger than the volume v required for the mutation by energy absorption considerations, under the assumption that this volume consists entirely of nucleic acid. We may conclude by

saying that *if the nucleic acid is responsible for the mutation of the tobacco mosaic virus, a substantial part of this acid existing in the virus, about one fourth, must be active in absorbing the energy needed for mutation.*

However if the protein were the only site of the primary mutational process, the volume involved would amount to

$$1.46 \times 10^{-6}/(5 \times 10^{-5} - 2.23 \times 10^{-6}) \approx 3\%$$

of the whole virus protein which would be still in agreement with the measurements of E. Pfankuch (1940) who concluded that at most 10% of the protein may be different in the tobacco mosaic virus and one of its variant, although the reliability of Pfankuch's electrophoretic method is put in doubt by C. A. Knight and M. A. Lauffer (1942).

It is seen in this way that the present analysis is not in disagreement with either of the two alternative theories as to the site of the primary mutational process (Stanley et al and Pfankuch et al). It may also be that both nucleic acid and the protein are involved in the mutation of the virus. W. M. Stanley and C. A. Knight (1941) suggested that the mutation of the virus may be a cumulative effect of events occurring during its multiplication and it is known from higher organisms that both nucleic acid and the protein are active during the cellular division (mitosis and meiosis, see e.g., H. Ris, 1947). In cases of somatic mutation differences in both these substances have been also encountered (cf. Caspersson and Santesson, 1942). It has been suggested however that a major part of the amino acids of the tobacco mosaic virus is not responsible for its activity and for its reproductive ability (Schramm and Müller, 1940; Miller and Stanley, 1941), whereas the nucleic acid seems to be essential for this purpose (Schramm, 1941).

The theory here applied implies that four ionizations in *any* place within the volume v produce the mutation of the virus. Since this volume (1.42 or 0.55 $\times$ 10^{-6} μ^3) is quite large on atomic scale the question arises how can four ionizations *anywhere* within this large group of atoms produce such a fine effect as a mutation from one type of virus to another one. A possible explanation of this could be seen in the fact that the protein molecule contains *many identical amino acid molecules so that a change in any of many of those molecules could produce the same effect.* Another explanation which has been suggested in similar circumstances is that the *energy has a great facility of transfer* from one place to another within the volume (Timoféeff-Ressovsky, 1937, p. 132). Quite convincing physicochemical examples of actual transfer of energy over volumes even larger

than this actually exist (Timoféeff-Ressovsky and Zimmer, 1947, pp. 107–117; Scheibe, 1941a). More specifically with reference to the tobacco mosaic viruses it is known that forces over distances of 100 Å and more act between them (Stanley, 1939); the fact that these viruses arrange themselves in a regular fashion even in weak solutions, so as to fill uniformly the available space with an interparticle distance up to 500 Å (Bernal and Fankuchen, 1941), is an excellent proof of forces acting between them over such distances, and where forces act energy is transmissible. Taking as the size of (v) even the larger figure 1.42×10^{-6} μ^3, each of the four ionizations would have to be effective within 0.355×10^6 Å^3, that is the energy available at each such event would have to travel in average perhaps not more than one-half of the diagonal of a cube of 0.355×10^6 Å^3 which is only 35.4 Å. However because of the oblong shape of the protein and of the nucleic acid molecules of the virus the energy may have to travel over distances more than this.

If instead of the whole virus, the nucleic acid alone were the site of the *primary* mutational process, a picturesque mechanism of transfer of energy would be possible. The determinations of the size and shape of the molecule of the nucleic acid of the tobacco mosaic virus have shown that this molecule (700 Å $\times$ 425 Å^2) is too long by a factor of several units to fit within the basic cell of the virus; nor can the nucleic acid molecules be arranged longitudinally along the virus, because their total length exceeds the available one by a factor of about 2 (Cohen and Stanley, 1942). The only possibility left is that the nucleic acid molecules are situated in a protruding fashion along the protein. This is confirmed by the fact that if the nucleic acid lie within the protein it would be recognizable there by means of X-rays because the absorption coefficient per unit of volume is more than two and one-half times as high for the nucleic acid as it is for the protein. Neither X-rays nor the electron microscope reveal the presence of such heavier molecules of the size of the nucleic acid within the virus (Cohen and Stanley, 1942). Further confirmation of this location of the nucleic acid may be seen also in the fact that an elimination of the nucleic acid from the virus by biochemical means (Schramm, 1941) does not split up its protein molecule. Now, if one imagines the nucleic acid molecules arranged in a parallel fashion *with respect to each other* (cf. Timoféeff-Ressovsky and Zimmer, 1947, p. 115; Butenandt et al, 1942), the virus would resemble a longitudinal bar to which several transversal bars are attached laterally; since these bars would be elastic an impact on one of them would put the others in vibration. This analogy could visualize the transfer of energy along the virus when an ionizing particle collides with one of the pro-

truding nucleic acid molecules. The fact that the number of these molecules in a virus is 8 (Cohen and Stanley, 1942) and that the number n of absorptions of energy sufficient for the mutation is 4 gives two possible pictures of the mechanism of mutation of the virus.

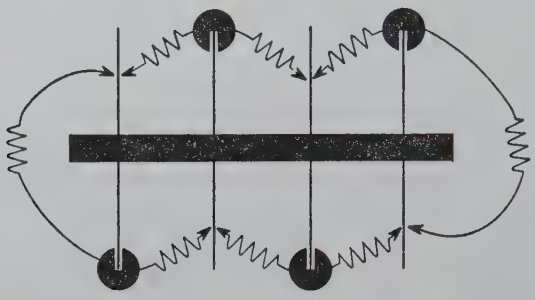

FIGURE 2. Schematical diagram of a protein molecule with 8 transversally arranged nucleic acid molecules making up the tobacco mosaic virus. The diagram illustrates how 4 impinging ionizing particles (represented by circles) can uniformly affect all 8 molecules through energy transfers (arrows) over distances not exceeding that of two closest neighbors. The theory implies that 4 ionizations suffice for the induction of mutation.

(a) If ionizing energy reaches a certain part of a nucleic acid molecule, a part of this energy is used for a structural change in this molecule and the remaining part is transferred to the neighboring nucleic acid molecules and possibly also to the protein molecule (Fig. 2). Because of the long distance between the neighbors, some 600 or 700 Å, the transfer of energy would be limited to the closest neighbors, and the energy reaching a nucleic acid molecule by such transfer would not be sufficient to produce in it the entire change necessary for the mutation; however if a sufficient amount of energy is transferred also from the other neighbor the whole change of that molecule necessary for the mutation would be accomplished. Although this transfer would occur over quite a substantial distance of 600 or 700 Å, it should be kept in mind that transfers of energy over much longer distances are also known to occur in physicochemistry (Riehl, 1941, p. 56; Scheibe, 1941b; Scheibe and Kandler, 1938; Möglich and Schön, 1938). This mechanism would imply that the mutation of the tobacco mosaic virus to the aucuba type requires a change in *all* the nucleic acid molecules of the virus.

(b) If a change in one-half of the number of molecules of the nucleic acid were sufficient for the particular mutation considered no transfer of energy between these molecules needs to be invoked.

The analysis can be carried out further by asking what part of the nucleic acid, if any, may be responsible for the mutation. If phos-

phorus is taken under consideration we obtain as the size of the volume (v):

$$v = 5.5 \times 10^{-7} \times 12.46 \times 1.6/150 = 7.31 \times 10^{-8}\ \mu^3,$$

because 150 cm^{-3} is the volume absorption coefficient of phosphorus at 1.5 Å. But the volume of phosphorus existing in the whole nucleic acid of the virus is

$$2.23 \times 10^{-6} \times 1.6 \times 0.0913/2.2 = 14.8 \times 10^{-8}\ \mu^3,$$

which is twice as much as v. Consequently, *changes in one-half of the phosphorus existing in the nucleic acid of the tobacco mosaic virus would be sufficient to produce its mutation to the aucuba type.* Such changes could involve for instance the phosphorus of every second molecule of the nucleic acid and would not require transfer of energy between various molecules of this acid. According to J. Johnson (1949) there are some twenty variants of the tobacco mosaic virus. Theoretically one cannot exclude the possibility that mutations to other variants imply the same type of mechanism, different molecules of the nucleic acid being involved in each case.

The table below summarizes the alternative conclusions of the analysis.

MUTATION OF THE TOBACCO MOSAIC VIRUS TO THE AUCUBA TYPE INDUCED BY 1.5 Å X-RAYS. POSSIBLE SITES OF THE PRIMARY MUTATIONAL PROCESS

Site (S)	Protein	Nucleic Acid	Phosphorus of the Nucleic Acid
Size of the volume (v) within which the primary process occurs	1.42×10^{-6} μ^3	5.5×10^{-7} μ^3	7.31×10^{-8} μ^3
Approximate ratio of the volume of (S) to the volume of (v)	35	4	2
Possible interpretation	(S) is a basic hexagonal cell unit as determined by X-Ray diffraction (Bernal and Fankuchen, 1941)	At least two molecules of the nucleic acid are affected by the process	Phosphorus in at least every second molecule of the nucleic acid is involved in the mutation

N. B. Calculations made on the basis of 5×10^{-5} μ^3 as the volume of the virus.

As much as this theory seems to agree with all the pertinent known facts about the tobacco mosaic virus there may be perhaps some doubt whether neglecting the inactivation of the aucuba viruses by the X-rays after they have been formed by this same radiation from the tobacco mosaic viruses is not a too crude approximation. In fact an inspection of the data of J. W. Gowen (1941) shows that the number of aucuba lesions obtained from an irradiated sample of the tobacco mosaic virus increases with the dosage up to a certain limit only to decrease thereafter. A possible explanation of this fact is the inactivation and to a small extent perhaps also mutation of some of the aucuba viruses which were previously formed from the tobacco mosaic viruses in the course of the same experiment. These *second order effects make the number* A *in equation* (7) *appear smaller than it would have been if one could take them into account.* We will see later that these effects are counterbalanced in part at least by the concentration effect. However before we consider the latter we proceed to a *type of analysis* in which different kind of second order effect *makes* A *appear larger* than it actually is.

(ii) In the previous analysis the inactivation of the aucuba viruses formed during the experimentation was neglected. An opposite type of approach is obtained by assuming that equal fractions of both the original tobacco mosaic viruses and the newly formed aucuba viruses are inactivated during the experimentation. Such approximation will make A/T appear *larger* than the value this ratio should have to correctly express the efficiency of X-rays as the mutating agent of the tobacco mosaic virus to the aucuba type. In fact the mutated viruses in their new aucuba form are obviously subject to a smaller amount of radiation than the original tobacco mosaic viruses. The implications of this assumption will now be analyzed. As to the reverse and other possible mutations of the aucuba viruses, we will neglect them as in (i) ; this can not change our conclusion that A/T appears here larger than it should because mutations are induced at a much smaller rate than inactivations.

The analysis is carried out here in a similar way as in (i) with the only difference that no survival probability needs to be considered since this is now assumed to be the same for both tobacco mosaic and aucuba viruses; instead of (7) the following relation is used now:

$$P(N_S + N_D) = A/T .$$

Figure 1 and the table give the results of calculations for $n = 1, 2, 3$. The standard deviation increases with n. An inspection of the figure shows also that the fit cannot be improved by increasing the value of n, because the experimental data indicate a pronounced con-

cavity downward whereas the theoretical curves have the opposite concavity for $n > 1$. In fact, formulae (9)—(10) show that the relationship between P and N_D is the incomplete gamma function $\gamma(vN_D\, n)$, except for the scale of ordinates and for a displacement of the origin of the system of coordinates. Because of the smallness of $P(N_S)$, such displacement does not change the concavity of the curve $P(N_D)$ in the present range at the origin. [For a graphical representation of the curves γ see e.g. P. Curie (1929), J. H. Webb (1948), J. Th. Van der Werff (1948), p. 135.] It is seen that the best fit that can be obtained with this theory is for $n = 1$. It is not satisfactory however since it gives a standard deviation for v of 15.7%, consequently on the basis of the latter the choice between the two analyses is easy since analysis (i) implies $\sigma = 2\%$. There is also another very important reason in favor of analysis (i): To produce the lesions the plant is infected by spreading the virus on the leaves. Now when the virus is used in high concentration there will be many cells which more viruses enter than it is necessary to produce a lesion (Caldwell, 1933). In the experiments of J. W. Gowen (1941), which are here analyzed, the tobacco mosaic virus was used in high concentration, whereas the aucuba virus obtained through mutation was in a very low concentration since most of the viruses of this sample were inactivated by the X-rays; consequently, as far as the concentration effect is concerned, A in equation (7) has its correct value corresponding to the number of aucuba viruses existing in the sample, whereas T appears smaller than it should. In this way A/T of that equation appears *larger* than it would have been if the concentration effects have been taken into account. But we know from a previous discussion of analysis (i) that A/T appears also *smaller* than it should because mutations and inactivation of aucuba viruses have been neglected in that analysis. In conclusion we may say that the approximations used in analysis (i) counteract and in analysis (ii) accentuate each other. We see in this way that *we have all the reasons to accept the results of analysis* (i) *against those of analysis* (ii).

Both types of analyses (i) and (ii) make it possible to calculate N_S from equation (11) after v and n have been determined. Using the results of analysis (i) we obtain $N_S = 282000$ or 729000 ionizations per μ^3 according to whether (v) is situated in the protein or in the nucleic acid. If the result of analysis (ii) were accepted it would give $N_S = 72400\ \mu^{-3}$. Two alternative interpretations of these figures are possible. Let us consider for instance $N_S = 500000$ as the average of the two figures of analysis (i). The cosmic radiations and the γ-rays from rocks amount to about 0.2 roentgen per year (see e.g. Compton, 1942), this gives in a round figure 1/2 ionizations per μ^3

per year. Consequently *if the spontaneous mutation were the exclusive work of naturally occurring ionizing energy the nature would have to work one million of years to do it! On the other side if the spontaneous mutation were carried out entirely in a single generation of the virus, mutating agents should naturally occur in the life of the virus more than one million times as powerful as the naturally existing ionizing energy,* since the length of a generation of a virus is a very small fraction of one year. It is difficult to see which one of these interpretations is closer to the truth, since our understanding of spontaneous mutations is very incomplete.

In the numerical calculations outlined in analyses (i) and (ii), the tables of the incomplete gamma function of E. C. Molina (1942) have been used. The tables of K. Pearson (1922) are less convenient because of a transformation of the argument which they involve. Since the mathematical problem in (i) and (ii) consists of calculating c from assigned values of n and of $\gamma = \gamma(c, n)$, the expansion of G. A. Campbell (1923) for the inversion of the incomplete gamma function by means of the probability integral could be also used instead of the tables of the γ-function.

The two analyses presented here each imply an opposite type of approximation; in the first analysis the inactivation of aucuba viruses formed during the experiment was neglected; in the second analysis the percentage of the same aucuba viruses inactivated has been assumed to be equal to the percentage inactivation of the original tobacco mosaic viruses. The exact situation lies somewhere between these two approximations. Which of them is better, it is difficult to say a priori. The first analysis shows a very outstanding agreement with the known experimental facts; this may be due to the concentration effect which counterbalances the approximation used in this analysis.

A mathematically more detailed type of analysis is outlined in the appendix. The paucity of experimental data does not justify carrying out this analysis more extensively.

Appendix

An analysis which takes into account the different average dosages which the two types of viruses must survive in order that the mutation be detected could be the following. Let $\exp(-k\,x)$ be the probability of a tobacco mosaic virus surviving as such a dose x, and $\exp(-h\,x)$ a similar probability for the aucuba virus. The exponential form of these probability functions is suggested to some extent by experimental data [cf. formula (6)]. If a tobacco mosaic

virus has survived as such a dose x its probability of mutation to aucuba with an additional dose dx is according to equation (5)

$$\delta = e^{-vx}(vx)^{n-1}d(xv)/(n-1)!$$

Consequently the probability of mutating a tobacco mosaic virus with a dose $\leq N_D$ and of detecting such mutation with the total dose $= N_D$ is

$$\begin{aligned} P(N_D) &= \int_{x=0}^{x=N_D} e^{-kx} \cdot \delta \cdot \exp\left[-(N_D - x)h\right] \\ &= v^n(v+k-h)^{-n}\gamma[(v+k-h)N_D, n]\exp(-N_D h). \end{aligned} \tag{12}$$

If the data on inactivation of the aucuba and the tobacco mosaic viruses of J. W. Gowen (1940, 1941) are plotted against the dosage quite a substantial dispersion appears. The expression

$$S = \exp(-5 \times 10^{-6} D) \tag{13}$$

for the probability of survival of each variant is about the best of exponential type. The dose D is here expressed in roentgen. Since this relation implies $h = k$, equation (12) becomes

$$P(N_D)/S(N_D) = \gamma(vN_D, n).$$

Taking into account the spontaneous mutation and assuming that there is no spontaneous inactivation the previous relation should be written:

$$P(N_D + N_S)/S(N_D) = \gamma(vN_D + vN_S, n).$$

Now, if the left-hand side of this equation is plotted against D using for S formula (13) and for $P(N_D + N_S)$ the ratio A_D/T_0 where T_0 is the number of the tobacco mosaic lesions obtained before administration of X-rays and A_D is the number of aucuba lesions obtained after administering a dose D to the tobacco mosaic virus, the curve obtained shows a pronounced maximum. This is incompatible with the form of γ which is a monotonously increasing function. The conclusion is that the assumption $h = k$, in particular relation (13), is a too crude approximation.

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BULLETIN OF
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SOME TYPES OF RELAXATION OSCILLATIONS AS MODELS OF ALL-OR-NONE PHENOMENA

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After some general remarks the results of the approximation method of Kryloff and Bogoliuboff are applied to show the existence of a threshold for a simple non-linear differential equation of a special form.

Many oscillation phenomena can be described, at least as a rather good approximation, by the differential equation

$$\ddot{x} + \alpha \dot{x} + \beta = 0 \tag{1}$$

in which the time-dependent variable x represents the deviation from the equilibrium position and α and β are constant with respect to the time t as well as to x. If α is positive the corresponding oscillation is damped and it dies out, while when α is negative the damping is negative and the amplitude of the deviation increases with the time t.

When the coefficients α and β are themselves functions of the variable x, the problem is somewhat more difficult. B. van der Poll (1930) has discussed the solution of the equation

$$\ddot{x} - \varepsilon(1 - x^2)\dot{x} + x = 0\,. \tag{2}$$

In the case $\varepsilon << 1$ he has shown analytically that for large values of t the solution of (2) becomes

$$x = 2\sin(t + \phi), \tag{3}$$

quite independent of the initial conditions; it represents a stationary or self-excited oscillation (van der Poll, 1930, Fig. 10). For the case $\varepsilon \geqslant 1$ van der Poll used the method of isoclines; he replaced (2) by the set of differential equations

$$\begin{aligned} \dot{x} &= y\,; \\ \dot{y} &= \varepsilon(1 - x^2)y - x\,; \end{aligned} \tag{4}$$

and plotted in an (x, y) diagram the curves along which $\frac{dy}{dx} =$ constant. By this method he noticed that the integral curves of equation (2) approach a fixed closed curve, quite independent of the initial conditions. These "limit cycles" of Poincaré represent also in this case a stationary periodic solution.

The coefficient of $\dot{x}$ in (2) is not constant, but a function of x, which is negative for values of x between $+1$ and -1, so that for those values of x the damping is negative. One might expect from this that the differential equation

$$\ddot{x} + \varepsilon(x-p)(x-q)\dot{x} + x = 0, \qquad (6)$$

in which p and q are both positive constants such that $p < q$, would also give a stationary periodic solution, independent of the initial conditions. If this was the case, the simple equation (6) would describe a threshold phenomenon. To illustrate this, notice that the coefficient of $\dot{x}$ in (6), and therefore the damping of the motion described by (6), is positive for $x < p$, but negative for $p < x < q$ and again positive for $x > q$. Therefore we get in an (x, t) diagram the next regions as shown in Figure 1. If the initial conditions are such that x

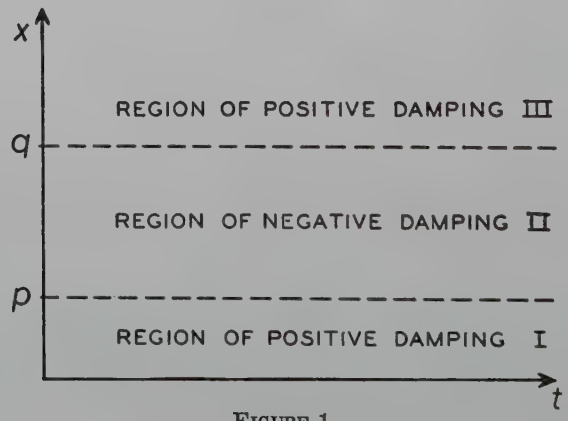

FIGURE 1

remains smaller than p, the oscillation is always positively damped and dies out. But if the initial conditions are such that the point in Figure 1 which represents the state of the system comes in region II, there might be a possibility, just as above with the negative damping

in the case of van der Poll, that a stationary oscillation, quite independent of the initial conditions, thus self-excited, exists. By combining the two last mentioned cases, we notice the possibility of the existence of an all-or-none phenomenon in the case of equation (6). However this is not the case. Though the only difference between (6) and van der Poll's equation (2) is that p in the former and in Figure 1 has changed its sign, this gives an essential difference. To show this we apply the result of a method developed by J. Sjohat (1944). He considers the more general equation:

$$\ddot{x} - \varepsilon F(x)\dot{x} + x = 0 . \tag{7}$$

Assuming that this equation has a periodic solution $x(t)$ with period T, he expands this function $x(t)$ in a Fourier series. Because

$$\int_0^T x dt = 0 ,$$

as can be seen by integrating (7) from $t = 0$ to $t = T$, the Fourier expansion of $x(t)$ can be written in the form

$$x(t) = \sum_{n=1}^{\infty} A_n \sin (n\nu t + \phi_n) , \tag{8}$$

Sjohat shows that the first term in this expansion gives a good approximation of $x(t)$. Therefore

$$x(t) \approx A_1 \sin(\nu t + \phi_1) . \tag{9}$$

Moreover he evaluates A_1 for the case in which $F(x)$ is a polynomial:

$$F(x) = \alpha_0 + \alpha_1 x + \cdots + \alpha_r x^r .$$

Under the assumption that equation (7) has a periodic solution $x(t)$ and for this form of $F(x)$ he finds that $z = A_1^2$ is approximately a root of the next equation:

$$\alpha_0 + \sum_{i=1}^{m} \alpha_{2i} \frac{1.3 \cdots (2i-1)}{2.4 \cdots 2i} \cdot \frac{z^i}{2i+1} = 0 , \tag{10}$$

in which m is the largest integer in $\frac{r}{2}$.

From this equation we see that equation (6) has no stationary oscillations as solutions, because in the case of that equation $r = 2$, $m = 1$ and α_0 and α_2 have the same sign. Therefore the necessary condition that (10) has at least one non-negative root cannot be satisfied. The reason for this failure becomes apparent by comparing this case

with that of van der Poll. In the latter case there is also a region of negative damping for negative values of x, namely that between 0 and -1, while in the former case the damping is positive for all negative values of x. Therefore the movement, when the deviation x has become smaller than p and afterward, becomes negative; it is

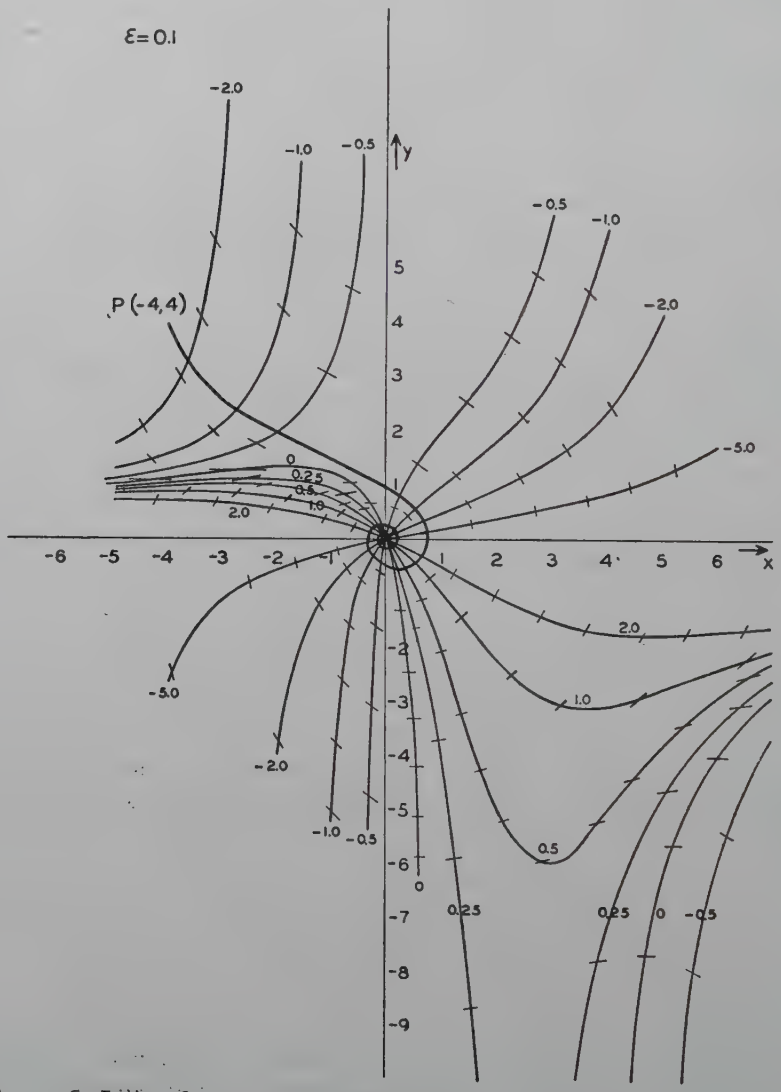

FIGURE 2. Integral curve of the equation

$$\ddot{x} + \varepsilon(x-1)(x-3)\dot{x} + x = 0$$

having the initial conditions $x_0 = -4$ and $\dot{x}_0 = 4$ for the case $\varepsilon = 0.1$.

so strongly damped that x does not exceed p again, even when it has done so once before. We have confirmed this presumption by using the method of isoclines (Fig. 2).

This explanation of the negative result has lead us to expect to get the description of a threshold phenomenon if the coefficient α of $\dot{x}$ in equation (1) is also negative for some negative values of x in such a way that for negative values of x also we have a situation as in Figure 1. In other words, we extend Figure 1 to the next figure. (Fig. 3). We will show that this is the case by examining the example

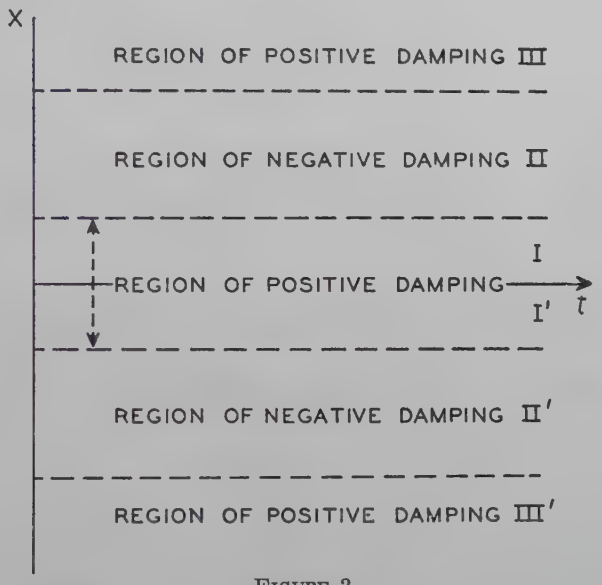

FIGURE 3

in which α in equation (1) is the next function of x:

$$\alpha = \varepsilon(x-1)(x+1)(x-3)(x+3),$$

or

$$\alpha = \varepsilon(x^4 - 10x^2 + 9).$$

Therefore, we will investigate the differential equation:

$$\ddot{x} + \varepsilon(x^4 - 10x^2 + 9)\dot{x} + x = 0. \qquad (11)$$

The graph of this function α of x has the form given in Figure 4. We will apply the method of Kryloff and Bogoliuboff (Minorsky, 1947). By this method it is shown that in the case of a more general equation than (6), namely

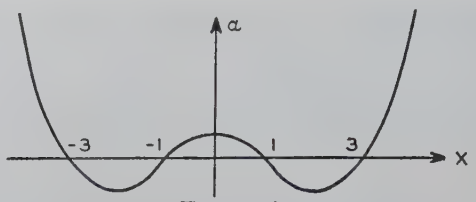

FIGURE 4

$$\ddot{x} + \varepsilon f(x, \dot{x}) + \omega^2 x = 0, \tag{12}$$

in which case $\varepsilon << 1$, the time-dependences of the amplitude a and the phase $\Phi = \omega t + \phi$ of the approximate solution

$$x = a \sin(\omega t + \phi),$$

are given by

$$\frac{da}{dt} = -\frac{\varepsilon}{\omega}\frac{1}{2\pi}\int_0^{2\pi} f(a \sin\psi, a\omega \cos\psi)\cos\psi d\psi, \tag{13}$$

and

$$\frac{d\phi}{dt} = \frac{\varepsilon}{a\omega}\frac{1}{2\pi}\int_0^{2\pi} f(a \sin\psi, a\omega \cos\psi)\sin\psi d\psi.$$

By applying (13) to our case of equation (11) in which we have $\omega = 1$ and

$$f(x, \dot{x}) = (x^4 - 10x^2 + 9)\dot{x},$$

therefore

$$f(a \sin\psi, a\omega \cos\psi) = (a^4 \sin^4\psi - 10a^2 \sin^2\psi + 9)a\omega \cos\psi.$$

We then get

$$\frac{da}{dt} = -\frac{\varepsilon}{\omega}\frac{1}{2\pi}\int_0^{2\pi} (a^4 \sin^4\psi - 10a^2 \sin^2\psi + 9)a\omega \cos^2\psi d\psi,$$

or (15)

$$\frac{da}{dt} = -\varepsilon\left(\frac{1}{16}a^5 - \frac{5}{4}a^3 + \frac{9}{2}a\right).$$

For a steady state we have

$$\frac{da}{dt} = 0,$$

and therefore in this case

$$\frac{1}{16}a^5 - \frac{5}{4}a^3 + \frac{9}{2}a = 0.$$

Hence $a_1 = 0$, $a_{2,3} = \pm 2.17$, $a_{4,5} = \pm 3.91$. Therefore there are two stationary oscillations possible, one with amplitude 2.17 and the other with amplitude 3.91.

From the following form, in which we can now write (15),

$$\frac{da}{dt} = -\frac{\varepsilon}{16}a(a^2 - 2.17^2)(a^2 - 3.91^2),$$

we see that

$$\text{For } 0 < a < 2.17 \qquad \frac{da}{dt} < 0$$

$$\text{For } 2.17 < a < 3.91 \qquad \frac{da}{dt} > 0$$

$$\text{For } a > 3.91 \qquad \frac{da}{dt} < 0.$$

Therefore there is in the case of equation (11) a stable stationary oscillation, which has the amplitude 3.91.

The frequency Ω of that oscillation can be calculated from (1) according to

$$\Omega = \frac{d\Phi}{dt} = \omega + \frac{d\phi}{dt}.$$

In the case of equation (11) this gives:

$$\Omega = \omega + \frac{\varepsilon}{a\omega}\frac{1}{2\pi}\int_0^{2\pi}(a^4 \sin^4\psi - 10a^2\sin^2\psi + 9)\, a\omega\cos\psi\cdot\sin\psi\, d\psi$$

$$= \omega = 1,$$

the integral being zero and $\omega = 1$ in equation (11). Therefore the frequency of the oscillation in the case of equation (11) is constant, as for the van der Poll equation (2). However in general the frequency will depend on the amplitude of the oscillation.

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BOOK REVIEW

J. Th. Van Der Werff. *Biological Reactions Caused by Electric Currents and by X-Rays.* 1948. xii + 203 pp. New York: Elsevier Publishing Company. (Printed in the Netherlands.) $5.00.

The fundamental idea in the background of this book is derived from some purely formal quantitative similarities between phenomena of electrical nerve excitation and radiobiological effects. Because of the complexity of these phenomena and our very rudimental knowledge of their biophysical nature it is difficult to say how much basic truth underlies such similarities. It is certain that the ionized state of matter is the primary intermediary of both processes. But to what extent is this common factor of importance? Certainly the energies involved are in both cases of a completely different order of magnitude; so far no nerve excitation by ionizing radiation has been reported, and in the clinical field electrotherapy and radiotherapy reveal completely different physiological mechanisms. The threshold concept, so firmly established in the electrophysiology of the nerve, seems to have a somewhat less fundamental importance in radiobiology. In fact, whereas for instance the erythema threshold is an accepted fact, the induction of mutations in Drosophila by X-rays, a most carefully investigated field of radiogenetics, does not reveal any threshold phenomenon.

R. M. Sievert (1941) was the first to formulate mathematically the existence of a reserve of a certain substance which has to undergo a certain change before the radiation may manifest its biological effect. If the energy administered is insufficient to carry out such a change no effect would appear. Along the same line of thought are the current suggestions that some biological effects of radiations consist of an inactivation of the existing supply of enzymes. The amount of this supply would then determine the magnitude of the threshold, if it exists.

The author starts his book by pointing out some formal analogies between:

(a) the Bunsen-Roscoe or Schwarzschild law and the relationship between the intensity of a constant current and its minimum time of application to cause a muscle contraction;

(b) the latency of several radiobiological phenomena and the persistency of certain effects in the nerve after the cessation of the cause as evidenced, for instance, by a succession of subliminal stimuli inducing nerve excitation;

(c) the oscillatory aspects of many phenomena of electrical nerve excitation, for instance the change in excitability due to short subliminal condenser discharges, and the oscillatory character of certain radiobiological processes stressed so much by A. Forssberg (1941, 1943) in his remarkable experiments on the effect of extremely small doses of X-rays (one thousandth of one roentgen) on the growth rate of the fungus *Phycomyces Blakesleeanus.*

This oscillatory character is known to occur in many other effects of radiation, of which the common erythema wave is perhaps the oldest although not the most evident example. Reporting these oscillations in the growth rate of irradiated root tips of *Vicia faba,* L. H. Gray (1949) suggested that this effect may be

apparent only due to some geometric peculiarities of growth of the irradiated material. However oscillatory character of radiobiological phenomena is known to exist in many other cases, and has been observed also in purely radiochemical processes such as irradiation of colloids (J. A. Crowther, H. Liebmann, R. Jones, C. C. Mills, 1936-1940). The recent experiments of B. E. Proctor and S. A. Goldblith (1949) on the change in the ultraviolet absorption spectrum of apricot extract and of 5- (hydroxymethyl) furfural with doses up to 20 million roentgen of cathode rays also show a clear indication of a beginning oscillation. The mechanism of such oscillations in radiobiology is not known; although suggestions for its explanation have been made (e.g. A. Forssberg). Oscillations in diffusion with intervening chemical reactions have been studied mathematically by several authors (D. G. Kendall, 1948; N. Rashevsky, 1948) and an attempt of their application to those still non-understood oscillatory radiobiological phenomena would seem to be a worthwhile enterprise.

Although the previously published work by the author lies in the field of theoretical radiobiology, two-thirds of the present book is neurophysiology. It is in the above-mentioned experiments of A. Forssberg and in the mathematical work of R. M. Sievert (1941) that the book had its origin. Both Sievert and Forssberg had a clear notion of the latency of the effects observed by them; this, combined with the assumption of an active reserve or ability of the organism to recover lead them to an interpretation of the oscillatory character of their experimental results. Following essentially the line of thought of these Swedish radiologists, the author assumes that the phenomena in both fields, the neurophysiological and the radiobiological, depend on the amount X of a certain substance ruled by a differential equation of the type

$$dX(t)/dt = -I(t-a)X(t) + L(t-b)Y(t), \tag{1}$$

where Y is understood essentially as the amount of the reserve substance, and I and L are coefficients describing the kinetics of two time-lag processes, as the form of the functions $I(t-a)$ and $L(t-b)$ indicates, t being the time and a, b the time-lags.

The neurophysiological part of the book is worked out mainly under the condition $Y =$ constant, which is Sievert's assumption. The two possibilities $a > b$ and $b > a$ are separately discussed. The author assumes

$$I(t) = (1 + c_1 i)I_0;\ L(t) = (1 + c_2 i)L_0; \tag{2}$$

at the cathode, and

$$I(t) = \frac{I_0}{1 + c_3 i};\qquad L(t) = \frac{L_0}{1 + c_4 i}; \tag{3}$$

at the anode, where i is the intensity of the current and the c_i's, I_0 and L_0 are constant. The author looks upon $I(t)$ and $L(t)$ as expressing the concentration of cations. He defines $L(t)/I(t)$ as the physiological electrotonus of the nerve. This definition plays an important part in the author's systematics of his theory; a large part of his study concerns the case in which $L(t)/I(t)$ is independent of i. Taking the smaller of the two quantities a, b as zero, which is equivalent to measuring the time from a suitable moment, the author's equation reduces to either one of the following two forms:

$$\begin{aligned} dx(t)/dt &= -I(t-a)x(t) + I(t); \\ dx(t)/dt &= -I(t)x(t) + I(t-a). \end{aligned} \tag{4}$$

The classical topics of electrical nerve excitation are discussed on the basis of these two equations. Since the latter are mixed differential and finite difference equations, they split up into four differential equations in the case of a constant current of finite duration. The functions $x(t)$ represent then a wave-like curve with three discontinuities of its tangent line. If the current lasts indefinitely a similar curve is obtained with $x = 0$ only at $t = \infty$ and one discontinuity of the tangent line. The relationship between the minimum duration of a constant current and the threshold intensity of the latter comes out to be the same as in Hill's theory. The author passes then to discuss the problem of condenser discharge through the nerve: he obtains essentially the same type of curve as with a constant current of finite duration, except that only one discontinuity of the tangent line appears. Here again the author obtains Hill's relation between the threshold voltage and the capacity and resistance. He then applies his equations to the accommodation phenomena in the case of linearly and exponentially increasing currents and discusses the problem of excitation at the anode by interrupting a constant current, under an arrangement in which a make excitation at the cathode is prevented. The relationship between the minimum intensity of the current and its duration necessary to obtain a break-excitation gives a finite duration for an infinite current which does not agree with Hill's formula, although the author contends that the experiments of Cardot and Laugier (1912, 1913) suggest the correctness of his mathematical result. He discusses then the case of a constant current with a gap. In the case of alternating currents the threshold intensity comes out directly proportional to the frequency for high frequencies and inversely proportional for low frequencies. The author stresses the possibility of describing by his equations the experiments of J. Erlanger and E. A. Blair (1931) on the change of excitability after a subliminal direct current has been put through the nerve, without discussing the question in detail, however. The experiments of W. A. H. Rushton and B. Katz on the decline of nerve excitability after short current pulses show some deviation from the author's theory. He discusses also A. Chweitzer's measurements (1937) on the change of rheobase after the passage of a current of constant intensity. His calculations do not give a minimum as flat as that obtained experimentally, however the probabilistic approach which he considers later leads to a better fit.

The author passes then to a brief treatment of the case in which his physiological electrotonus depends on the intensity of the current, that is when the c_i's in equations (2) and (3) are different from each other. This approach leads in many cases to no essentially new conclusions. Since a careful discussion of the two cases $a \leqslant b$ gives fundamentally the same results, the author sees no way of deciding which one of the two inequalities actually holds. He seems to be particularly concerned with the following contradiction between experimental findings and a consequence of the theory presented by him in the first hundred pages of the book: the ratio λ of the rheobasic current i to the minimum value of di/dt causing nerve excitation comes out to be smaller than a or b in the case of an exponentially increasing current, whereas from an analysis of the experimental data it follows that it should be larger.

To eliminate this and other discrepancies the author generalizes his theory by assuming that the functions $I(t)$ and $L(t)$ which characterize the nerve excitability represent cumulative effects of a number of random events according to the Poisson distribution. Under this assumption the mathematics becomes quite complicated. Some of the relations which the author obtains by this new theory, insofar as numerically analyzed by him, do not differ qualitatively from the preceding

ones, except that no angular points appear on his curves. Quantitatively, however, there are cases which give by this theory essentially different results and this seems to be the reason why the author considered this modification of his previous approach. For instance, prevention of excitation after an overthreshold current pulse has been applied, by means of a strong current pulse in the opposite direction immediately after the first pulse (Rushton and Katz) can be described by this theory but not by the preceding ones. Similarly Hill's factor λ is now not necessarily smaller than the rheobasic utilization time, as the previous theory indicated. The theory of Chweitzer's experiments now gives a flatter minimum than before. The author claims that this is the only mathematical account of Chweitzer's results known up to now.

The last part of the book is entitled "Biological Reactions Caused by X—and γ—Rays." It is not clear to the reviewer why the author restricts the title to these two forms of radiation only. Since his theory is descriptive and formal there seems to be no reason for discrimination between the various types of radiations, including ultraviolet and even the visible range. The author's paper of 1942 was an expansion of Sievert's mathematical concepts and the radiobiological part of the present book is a further development of these ideas. A whole chapter deals with an interpretation of Forssberg's experiments by means of an equation of type (1). The remaining chapters discuss other radiobiological experiments revealing oscillatory character. In considering the relation $it^p = \text{constant}$ between radiation intensity i and the time t of its application necessary to achieve a certain effect, the author interprets the case $p < 1$ as due to recovery phenomena which are more efficient at lower radiation intensities if the total administered energy is the same. He interprets the case $p > 1$ in the following way:

> With an irradiation of very short duration only certain cells, being in a very radio-sensitive phase, may be killed. With an irradiation of longer duration there may be more chance that other cells come into that radio-sensitive phase and so the effect may be enlarged by diminishing the intensity.

If the radiation acts through a catalyst, the effects of radiation will depend not only on the amount of this catalyst but also on the time during which it is active. This interpretation of $p > 1$ has been suggested by the reviewer (1947) as a possible explanation of the relation $it^2 = \text{constant}$ found by A. M. Brues, H. Lisco and M. Finkel (1946) for the induction of bone sarcoma in mice by a radioactive isotope of strontium. It should be kept in mind however that no direct evidence of the existence of such catalyst has been obtained up to now.

The book closes with brief discussions of the Bunsen-Roscoe law, the cumulative dosage concept, the F. Dessauer—M. Blau—K. Altenburger approach to radiation effects through the cumulative Poisson distribution (1922). As a whole the radiobiological part appears to be treated in a rather sketchy form, if one compares it with the systematic and quite detailed mathematical work presented by the author in the part dealing with the electrical nerve excitation. The reason for this lies probably in the much more pronounced complexity of radiobiological phenomena as compared with the relatively simpler situations met in exciting electrically a nerve in vitro. Contrary to the author's impression he uses mathematics for a quantitative description and not for a physical explanation of the observations. A comparison of the radiobiological part of his book with D. E. Lea's "Actions of Radiations on Living Cells" may give an idea to what extent the

reviewer's viewpoint is correct. However the history of science shows that a new theory starts sometime with formal, somewhat abstract and purely descriptive concepts before acquiring a concrete reality in terms of experimentally known facts. From this viewpoint the book may be a very interesting one, and is certainly suggestive of many ideas deserving further thought.

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